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2 3 4 5 6 7 8 9 18 17 16 15 14 13

Table of Contents

Immunology

Chapter 1 Overview of Immunity 1-1
1 Components of the Immune System 1-1
2 The Design of the Immune System 1-2

Chapter 2 The Birth of the Immune Response 2-1
1 Origin of Immune Cells 2-1
2 The Cells of the Immune System 2-2
3 Development of Antigen Recognition Molecules 2-4
4 Selection of Lymphocyte Receptors 2-10

Review Questions: Chapters 1–2 2-16

Chapter 3 Immunologic Surveillance: Lymphocyte Recirculation 3-1
1 Overview of Lymphocyte Recirculation 3-1
2 Secondary Lymphoid Organs 3-2

Chapter 4 The Battle Begins: Acute Inflammation 4-1
1 Overview of Acute Inflammation 4-1
2 Chemotaxis 4-1
3 Diapedesis 4-2
4 Recognizing Nonself 4-4
5 Phagocytosis 4-5

Chapter 5 Processing and Presentation of Antigens 5-1
1 Overview of Antigen-Presenting Cells 5-1
2 Pathways for Loading MHC Molecules With Peptides 5-1
3 Transportation of Antigen to Secondary Lymphoid Organs 5-3
4 Differentiation of Macrophage Populations 5-4
5 Activation of T Helper Cells 5-5
6 Differentiation of T Helper Cell Subsets 5-7

Review Questions: Chapters 3–5 5-10

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Table of Contents

Immunology

Chapter 6 Humoral Immunity 6-1

1 Overview of Humoral Immunity 6-1
2 T Cell Independent B Cell Activation 6-1
3 T Cell Dependent B Cell Activation 6-3
4 Class Switching 6-4
5 Affinity Maturation 6-7
6 Isotype Switching 6-8
7 Complement 6-11

Chapter 7 Cell-Mediated Immunity 7-1

1 Overview of Cell-Mediated Immunity 7-1
2 Effector Cells of CMI 7-2

Chapter 8 Immunologic Memory 8-1

1 Overview of Immunologic Memory 8-1
2 Activation-Induced Cell Death 8-1
3 Characteristics of Memory Cells 8-2
4 Dissemination of Memory 8-2
5 Comparison of Primary and Subsequent Immune Responses 8-3

Review Questions: Chapters 6–8 8-4

Chapter 9 Immunoprophylaxis and Immunotherapy 9-1

1 Forms of Immunologic Therapy 9-1
2 Active Immunization 9-2
3 Passive Immunotherapy 9-6

Chapter 10 Immunodeficiency Diseases 10-1

1 Primary Immunodeficiencies 10-1
2 Acquired Immunodeficiencies: HIV/AIDS 10-5

Review Questions: Chapters 9–10 10-7

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Table of Contents

Immunology

Chapter 11 Hypersensitivity and Autoimmunity 11-1

1 Overview of Hypersensitivity and Autoimmunity 11-1
2 Type I Hypersensitivity 11-2
3 Type II Hypersensitivity 11-5
4 Type III Hypersensitivity 11-7
5 Type IV Hypersensitivity 11-8
6 Pathogenesis of Autoimmunity 11-9
7 Therapy of Hypersensitivities and Autoimmune Diseases 11-10

Chapter 12 Transplantation Immunology 12-1

1 Overview of Transplantation Immunology 12-1
2 Mechanisms of Transplant Rejections 12-2
3 Tissue Compatibility Testing 12-6

Chapter 13 Uses of Immunology in Diagnostic Medicine 13-1

1 Precipitation and Agglutination Reactions 13-1
2 Immunofluorescent Assays 13-3
3 Radioimmunoassay (RIA) and Enzyme-linked Immunoassay (EIA) 13-4
4 Western Blot 13-5
5 Fluorescence-Activated Cell Sorter 13-6

Review Questions: Chapters 11–13 13-7

Clinical Cases C-1

Appendix 1 Cytokines A-1

Appendix 2 CD Markers A-3

Appendix 3 Cell Adhesion Molecules A-4

Appendix 4 The Immune Response in Infection A-5

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Table of Contents

Immunology Figures

Chapter 1 Overview of Immunity

Figure 1-2.0 . . . Overview of the Immune System 1-3

Chapter 2 The Birth of the Immune Response

Figure 2-1.0 . . . Bone Marrow Origin of Immune Cells 2-1
Figure 2-3.0 . . . Antigen Receptors of B and T Lymphocytes 2-4
Figure 2-3.1 . . . Structure of Immunoglobulin (BCR) 2-5
Figure 2-3.2 . . . B and T Cell Signal Transduction Complexes 2-6
Figure 2-3.3A . . Heavy Chain Rearrangements 2-8
Figure 2-3.3B . . Light Chain Rearrangements 2-8
Figure 2-3.5 . . . Germline DNA Sequence in B Cells 2-9
Figure 2-4.1 . . . B Lymphocyte Ontogeny 2-10
Figure 2-4.2A . . Architecture of the Thymus 2-11
Figure 2-4.2B . . Structure and Complementarity of MHC Class 1 and 2 2-12
Figure 2-4.2C . . T Cell Selection in the Thymus 2-14
Figure 2-4.2D . . The Ontogeny of T Cells 2-15

Chapter 3 Immunologic Surveillance: Lymphocyte Recirculation

Figure 3-2.1 . . . Anatomy of the Lymph Node 3-2
Figure 3-2.2 . . . Anatomy of the Spleen 3-3

Chapter 4 The Battle Begins: Acute Inflammation

Figure 4-3.4A . . Steps of Leukocyte Extravasation 4-2
Figure 4-3.4B . . Acute Inflammatory Response 4-3
Figure 4-4.2 . . . Toll-Like Receptors 4-4
Figure 4-5.1 . . . Phagocytosis 4-5
Figure 4-5.3A . . Mechanisms of Intracellular Killing 4-6
Figure 4-5.3B . . Intracellular Killing in CGD 4-7

Chapter 5 Processing and Presentation of Antigens

Figure 5-2.2 . . . Major Histocompatability Complex 5-2
Figure 5-3.0 . . . Antigen Transport to Secondary Lymphoid Organs 5-3
Figure 5-4.0 . . . Macrophage Subpopulations 5-4

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Table of Contents

Immunology Figures

Figure 5-5.0A . . T Cell Activation 5-5
Figure 5-5.0B . . Superantigens 5-6
Figure 5-6.0A . . T-Cell Subpopulations 5-8
Figure 5-6.0B . . Th Subpopulations 5-9

Chapter 6 Humoral Immunity

Figure 6-3.0 . . . T Cell Dependent B Cell Activation 6-3
Figure 6-4.1A . . Pepsin Cleavage of Ig 6-4
Figure 6-4.1B . . Papain Cleavage of Ig 6-5
Figure 6-4.2 . . . IgM Structure 6-6
Figure 6-5.1 . . . Affinity vs. Avidity 6-7
Figure 6-5.2 . . . Clonal Selection of B Cells 6-7
Figure 6-6.1 . . . Germline DNA Rearrangements 6-8
Figure 6-6.2 . . . IgG Structure 6-9
Figure 6-6.3A . . IgA Structure 6-9
Figure 6-6.3B . . Secretory IgA 6-10
Figure 6-7.1 . . . Alternative, Classical, and Lectin Pathways 6-11
Figure 6-7.2A . . Complement Split Products 6-12
Figure 6-7.2B . . Summary of Humoral Immunity 6-13

Chapter 7 Cell-Mediated Immunity

Figure 7-1.0 . . . Nirvana 7-1
Figure 7-2.2 . . . Cytotoxic T Lymphocytes 7-2
Figure 7-2.3 . . . Natural Killer Cells 7-3
Figure 7-2.4 . . . ADCC 7-4

Chapter 8 Immunologic Memory

Figure 8-5.0 . . . Primary vs. Secondary Immune Responses 8-3

Chapter 9 Immunoprophylaxis and Immunotherapy

Figure 9-2.0 . . . CDC Schedule of Vaccinations 9-2
Figure 9-2.1 . . . The Hapten-Carrier Effect in Conjugate Vaccines 9-3
Figure 9-2.4 . . . Immunoglobulins in Fetus and Newborn Infant 9-5

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Table of Contents

Immunology Figures

Chapter 10 Immunodeficiency Diseases

Figure 10-1.4A . DiGeorge Syndrome 10-3
Figure 10-1.4B . Wiskott-Aldrich Syndrome 10-3
Figure 10-1.5 . . Immunodeficiency Diseases and Developmental Blocks 10-4
Figure 10-2.2A . Course of Untreated HIV 10-5
Figure 10-2.2B . HIV Effects on Immune System 10-6

Chapter 11 Hypersensitivity and Autoimmunity

Figure 11-2.1 . . Development of Type 1 Hypersensitivity 11-2
Figure 11-2.2 . . Type 1 Hypersensitivity Mediators 11-4
Figure 11-3.2A . Hemolytic Disease of the Newborn 11-5
Figure 11-3.2B . Graves Disease 11-6
Figure 11-3.2C . Myasthenia Gravis 11-6
Figure 11-3.2D . Pathogenesis of Graves Disease (Type II) vs. Hashimoto Thyroiditis (Type IV) 11-6
Figure 11-3.2E . Pathogenesis of Myasthenia Gravis 11-6
Figure 11-4.2A . Lupus 11-7
Figure 11-4.2B . Scleroderma 11-7
Figure 11-4.2C . CREST 11-7
Figure 11-5.2A . Rheumatoid Arthritis 11-8
Figure 11-5.2B . Brain Scan—Multiple Sclerosis 11-8
Figure 11-5.2C . Pernicious Anemia 11-8
Figure 11-7.0 . . Helper T Cells and Hypersensitivities 11-11

Chapter 12 Transplantation Immunology

Figure 12-2.0 . . Transplant Rejection 12-2
Figure 12-2.1A . Hyperacute Rejection 12-3
Figure 12-2.1B . Acute Rejection 12-3
Figure 12-2.1C . Chronic Rejection 12-4
Figure 12-3.1 . . ABO Blood Typing 12-6
Figure 12-3.2 . . Microcytotoxicity Test 12-7
Figure 12-3.3 . . Mixed Lymphocyte Reaction (MLR) 12-8

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Table of Contents

Immunology Figures

Chapter 13 Uses of Immunology in Diagnostic Medicine

Figure 13-1.1 . . Agglutination and Precipitation Titration Curve 13-1
Figure 13-1.2 . . Coombs Test 13-2
Figure 13-2.1 . . Direct Fluorescent Antibody Test 13-3
Figure 13-2.2 . . Indirect Fluorescent Antibody Test 13-3
Figure 13-3.0 . . Enzyme Immunoassay 13-4
Figure 13-4.0 . . Western Blot Test. 13-5
Figure 13-5.0 . . Flow Cytometry With FACS 13-6

Clinical Cases

Figure C-1 . . . . . Omenn Syndrome C-1
Figure C-3A . . . . Killing Within the Phagocyte C-4
Figure C-3B . . . . Intracellular Killing in CGD C-5
Figure C-3C . . . . Nitroblue Tetrazolium Reduction C-6

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Table of Contents

Immunology Tables

Chapter 1 Overview of Immunity

Table 1-1.2 Components and Characteristics of the Immune System 1-2

Chapter 2 The Birth of the Immune Response

Table 2-2.0A Myeloid-Origin Cells 2-2

Table 2-2.0B Lymphoid Origin Cells. 2-3

Table 2-3.2 Comparison of B and T Cell Antigen Receptors 2-7

Table 2-3.4 B and T Cell Receptor Gene Rearrangements. 2-9

Table 2-4.2 Summary of HLA Structure and Expression. 2-13

Chapter 4 The Battle Begins: Acute Inflammation

Table 4-2.0 Chemotaxins. 4-1

Chapter 5 Processing and Presentation of Antigens

Table 5-2.2 MHC Class 1 and MHC Class 2 5-2

Table 5-6.0 Summary of Th Subsets 5-8

Chapter 6 Humoral Immunity

Table 6-6.3 Antibody Isotype Functions. 6-10

Chapter 7 Cell-Mediated Immunity

Table 7-2.0 Effector Mechanism Characteristics 7-4

Chapter 8 Immunologic Memory

Table 8-3.0 Naive, Effector, and Memory Lymphocytes 8-2

Chapter 9 Immunoprophylaxis and Immunotherapy

Table 9-1.0 Types of Immunity. 9-1

Table 9-2.1 Bacterial Vaccines 9-2

Table 9-2.2 Viral Vaccines 9-4

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Table of Contents

Immunology Tables

Chapter 10 Immunodeficiency Diseases

Table 10-1.1 Phagocyte Defects 10-1
Table 10-1.2 Humoral Immune Defects 10-2
Table 10-1.3 Complement Deficiencies 10-2
Table 10-1.4A T Lymphocyte Defects. 10-3
Table 10-1.4B Combined Partial B and T Cell Deficiencies 10-3
Table 10-1.5 Severe Combined Immunodeficiencies (SCIDs) 10-3

Chapter 11 Hypersensitivity and Autoimmunity

Table 11-1.0 Types of Hypersensitivity 11-1
Table 11-2.2A Type I Hypersensitivity Mediators. 11-3
Table 11-2.2B Type I Hypersensitivities 11-3
Table 11-3.2A Cytotoxic Type II Hypersensitivities 11-5
Table 11-3.2B Non-Cytotoxic Type II Hypersensitivities 11-6
Table 11-4.2A Type III Hypersensitivities. 11-7
Table 11-4.2B Autoantibodies Associated with Hypersensitivity Diseases 11-7
Table 11-5.2 Type IV Hypersensitivities 11-8
Table 11-6.2 HLA Disease Associations 11-9
Table 11-7.0A Monoclonal Antibody Therapies 11-10
Table 11-7.0B Summary of Type I–IV Hypersensitivities 11-10

Appendix 1 Cytokines

Table A-1.1 Cytokines A-1
Table A-1.2 Cytokines Available in Recombinant Form A-2

Appendix 2 CD Markers

Table A-2.1 CD Markers. A-3

Appendix 3 Cell Adhesion Molecules

Table A-3.1 Cell Adhesion Molecules A-4

Appendix 4 The Immune Response in Infection

Table A-4.1 The Immune Response in Infection A-5

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Table of Contents

Microbiology

Chapter 1 Microbial Pathophysiology 1-1

1 Comparative Anatomy and Physiology of Infectious Agents 1-1
2 Normal Flora 1-2
3 Mechanisms of Pathogenicity 1-3

Chapter 2 Bacterial Genetics and Drug Resistance 2-1

1 The "Dogma of Life" 2-1
2 Bacterial Genetic Material 2-3
3 Stabilization of Donated DNA 2-4
4 Gene Transfer 2-6
5 Drug Resistance 2-18
6 Antibiotic Susceptibility Testing 2-24

Review Questions: Chapters 1–2 2-27

Chapter 3 Bacteriology 3-1

1 Structure and Morphology 3-1
2 Physiology 3-5
3 Laboratory Techniques 3-7
4 Overview of the Medically Important Bacteria 3-9
5 Gram-Positive Cocci 3-10
6 Gram-Positive Rods 3-19
7 Gram-Negative Cocci 3-31
8 Gram-Negative Rods 3-34
9 Spirochetes 3-52
10 Unusual Bacteria 3-56
11 Mycoplasmataceae 3-60

Chapter 4 Virology 4-1

1 Biology of Viruses 4-1
2 Hepatotropic Viruses 4-16
3 DNA Viruses 4-20
4 Positive-Sense RNA Viruses 4-32

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Table of Contents

Microbiology

5 Negative-Sense RNA Viruses 4-46
6 Double-Stranded RNA Viruses 4-55
7 Prions 4-56

Review Questions: Chapters 3–4 4-57

Chapter 5 Mycology 5-1
1 Biology of Fungi 5-1
2 Superficial and Subcutaneous Mycoses 5-5
3 Systemic Mycoses 5-8
4 Opportunistic Mycoses 5-11

Chapter 6 Parasitology 6-1
1 Biology of Parasites 6-1
2 Protozoa 6-3
3 Helminth Parasites 6-9

Review Questions: Chapters 5–6 6-14

Appendix 1 Taxonomic Charts A-1

Appendix 2 Collected Concepts for Memorization A-19

Appendix 3 Organ/System-Based Infectious Diseases Charts A-31
Dermatology A-31
Hematology A-44
Bone and Joint A-48
Eye A-51
Ear, Nose, Throat, and Respiratory A-55
Central Nervous System A-66
Cardiac A-74
Gastrointestinal A-77
Urinary/Renal A-88
Reproductive A-92

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Table of Contents

Microbiology Figures

Chapter 1 Microbial Pathophysiology

Figure 1-3.6 . . . Endotoxin Action 1-7

Chapter 2 Bacterial Genetics and Drug Resistance

Figure 2-1.0A . . Dogma of Life: Microbial Modifications 2-1
Figure 2-1.0B . . DNA and RNA Polymerases 2-2
Figure 2-1.0C . . Endonucleases. 2-2
Figure 2-1.0D . . Exonucleases 2-2
Figure 2-1E . . . . Alleles 2-2
Figure 2-3.1 . . . Homologous Recombination 2-4
Figure 2-3.2 . . . Site-Specific Recombination 2-5
Figure 2-4.1 . . . Gene Transfer 2-6
Figure 2-4.2A . . Transformation 2-6
Figure 2-4.2B . . Fertility Factor 2-7
Figure 2-4.2C . . Bacterial Mating Types 2-8
Figure 2-4.2D . . $F^+ \times F^-$ Conjugation 2-9
Figure 2-4.2E . . The Hfr Chromosome 2-10
Figure 2-4.2F . . Conjugation 2-11
Figure 2-4.2G . . The Hfr $\times$ F^- Cross 2-12
Figure 2-4.2H . . Generalized Transduction 2-13
Figure 2-4.2I. . . Integration 2-14
Figure 2-4.2J. . . Normal Excision. 2-15
Figure 2-4.2K . . Error of Excision 2-15
Figure 2-4.2L . . Specialized Transduction. 2-16
Figure 2-5.3A . . Plasmid-Encoded Drug Resistance Mechanisms 2-19
Figure 2-5.3B . . Accumulation of Drug Resistance Genes 2-20
Figure 2-5.3C . . Transposition. 2-21
Figure 2-5.3D . . Resistance Transfer Factor 2-22
Figure 2-5.3E . . Selection of Resistance Strains 2-22
Figure 2-6.1 . . . Kirby-Bauer Agar Disc Diffusion Test 2-24
Figure 2-6.2 . . . Determination of the Minimal Inhibitory and Minimal Bactericidal Concentrations 2-25

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Table of Contents

Microbiology Figures

Please visit us at www.Groupinsiders.com

Chapter 3 Bacteriology

Figure 3-1.1A . . Gram-Positive Cell Envelope 3-1
Figure 3-1.1B . . Gram-Negative Cell Envelope 3-2
Figure 3-1.1C . . Location of Antibacterial Action 3-2
Figure 3-1.2 . . . Endospore. 3-4
Figure 3-2.1 . . . Four Phases of Bacterial Growth 3-5
Figure 3-3.1A . . Gram-Positive and Gram-Negative Bacilli 3-7
Figure 3-3.1B . . Acid-Fast Bacilli 3-8
Figure 3-4.0 . . . Bacterial Taxonomy 3-9
Figure 3-5.0 . . . Laboratory Algorithm: Gram-Positive Cocci 3-10
Figure 3-5.1 . . . Gram-Positive Cocci in Clusters: *Staphylococcus* 3-10
Figure 3-5.2A . . Gram-Positive Cocci in Chains 3-12
Figure 3-5.2B . . Patterns of Hemolysis. 3-12
Figure 3-5.2C . . Laboratory Algorithm: *Streptococcus* 3-13
Figure 3-5.2D . . CAMP Test: Positive for GBS (*left*) and Negative for GBS (*right*) . . 3-16
Figure 3-5.2E . . Lancet-Shaped Diplococcus: Pneumococcus 3-17
Figure 3-5.2F . . Alpha Hemolysis (Middle Streak) 3-17
Figure 3-5.2G . . Mucoid Colonies: Encapsulated 3-17
Figure 3-5.2H . . Colon Cancer Lesion. 3-18
Figure 3-6.0 . . . Laboratory Algorithm: Gram-Positive Rods 3-19
Figure 3-6.1A . . *Bacillus anthracis*. 3-20
Figure 3-6.1B . . Anthrax Eschar 3-20
Figure 3-6.1C . . Mediastinal Widening in Pulmonary Anthrax 3-20
Figure 3-6.1D . . *Clostridium* 3-21
Figure 3-6.1E . . Risus Sardonicus 3-21
Figure 3-6.1F . . Opisthotonus. 3-21
Figure 3-6.1G . . Nagler Reaction 3-23
Figure 3-6.1H . . Endoscopy of Colon with Pseudomembranous Colitis 3-23
Figure 3-6.2A . . Diphtheria Pseudomembrane. 3-24
Figure 3-6.2B . . Tellurite Agar. 3-24
Figure 3-6.2C . . *Listeria monocytogenes* 3-25
Figure 3-6.3A . . Actinomycotic Mycetoma 3-26
Figure 3-6.3B . . Partially Acid-Fast: *Nocardia* 3-26
Figure 3-6.3C . . Nocardial Mycetomas 3-26

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Table of Contents

Microbiology Figures

Figure 3-6.4A . . Mycobacterial Cell Envelope 3-27
Figure 3-6.4B . . Tuberculous Meningitis 3-27
Figure 3-6.4C . . Acid-Fast Bacilli: *Mycobacterium* 3-27
Figure 3-6.4D . . Tubercular Granuloma 3-27
Figure 3-6.4E . . Progression of Tuberculosis 3-28
Figure 3-6.4F . . Positive Tuberculin Test. 3-28
Figure 3-6.4G . . Primary TB: The Ghon Complex. 3-28
Figure 3-6.4H . . Lepromatous Leprosy 3-29
Figure 3-7.0 . . . Laboratory Algorithm: Gram-Negative Cocci 3-31
Figure 3-7.1A . . Gram-Negative Diplococci: *Neisseria* 3-31
Figure 3-7.1B . . Meningococcal Disseminated Intravascular Coagulopathy 3-32
Figure 3-7.1C . . Waterhouse-Friderichsen Syndrome (Adrenals) 3-32
Figure 3-7.1D . . Gonococcal Urethritis 3-33
Figure 3-7.1E . . Gonococcal Cervicitis 3-33
Figure 3-7.1F . . Gonococcal Ophthalmia Neonatorum 3-33
Figure 3-8.0 . . . Laboratory Algorithm: Gram-Negative Bacilli. 3-34
Figure 3-8.1A . . Stages of Whooping Cough 3-35
Figure 3-8.1B . . Whooping Cough 3-35
Figure 3-8.1C . . Ulceroglandular Tularemia. 3-36
Figure 3-8.1D . . Encapsulated Gram-Negative Rods: *Pseudomonas* 3-38
Figure 3-8.1E . . Ecthyma Gangrenosum. 3-38
Figure 3-8.1F . . *Campylobacter jejuni* 3-39
Figure 3-8.1G . . Sites of *Helicobacter* lesions 3-40
Figure 3-8.1H . . Gram-Negative, Comma-Shaped Rods: *Vibrio* 3-40
Figure 3-8.1I. . . Gram-Negative Pleomorphic Rods: *Haemophilus* 3-41
Figure 3-8.1J. . . Steeple Sign 3-42
Figure 3-8.1K . . Chancroid 3-42
Figure 3-8.2A . . Laboratory Algorithm: Gram-Negative Rods: Oxidase Negative . 3-44
Figure 3-8.2B . . Metallic Green Sheen on Eosin Methylene Blue Agar. 3-44
Figure 3-8.2C . . *Escherichia Coli* Gram Stain 3-45
Figure 3-8.2D . . Mucoid Growth of *Klebsiella pneumoniae* 3-46
Figure 3-8.2E . . Staghorn Renal Calculus 3-46
Figure 3-8.2F . . Disseminated Intravascular Coagulation From Plague. 3-50

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Microbiology Figures

Figure 3-8.2G . . Bubonic Plague Buboes. 3-50
Figure 3-9.0 . . . Laboratory Algorithm: Atypical Bacteria 3-52
Figure 3-9.2 . . . Darkfield Microscopy of *Treponema pallidum*. 3-52
Figure 3-9.3A . . *Borrelia burgdorferi* 3-54
Figure 3-9.3B . . *Ixodes dammini* (3 instars) 3-54
Figure 3-9.4 . . . *Leptospira interrogans* 3-55
Figure 3-10.1A . Chlamydia Life Cycle 3-56
Figure 3-10.1B . Chlamydial Reticulate Bodies. 3-57
Figure 3-10.2 . . *Rickettsia rickettsii*. 3-59

Chapter 4 Virology

Figure 4-1.1A . . Viral Morphology 4-1
Figure 4-1.1B . . Life Cycle of Positive-Sense and Negative-Sense RNA Viruses . . . 4-2
Figure 4-1.1C . . Viral Shapes and Sizes 4-3
Figure 4-1.2A . . Viral Life Cycle. 4-4
Figure 4-1.2B . . Viral Attachment 4-5
Figure 4-1.2C . . Direct Fusion (*left*) and Viropexis (*right*). 4-5
Figure 4-1.2D . . Viral mRNA Synthesis. 4-6
Figure 4-1.2E . . Viral Release 4-7
Figure 4-1.3A . . Courses of Viral Infection 4-8
Figure 4-1.3B . . Viral Infections: Age Most Commonly Infected 4-9
Figure 4-1.3C . . Interferon Production 4-10
Figure 4-1.4A . . Antigenic Shift. 4-11
Figure 4-1.4B . . Phenotypic Mixing 4-11
Figure 4-1.4C . . Phenotypic Masking 4-12
Figure 4-1.4D . . Complementation 4-12
Figure 4-1.5 . . . Viral Oncogenesis and Cell Cycle Regulation 4-14
Figure 4-1.6 . . . Mechanism of Action and Antiviral Drugs 4-15
Figure 4-2.2 . . . Complete Infectious Virion (Dane Particle) 4-17
Figure 4-2.3A . . Acute Hepatitis B Serology 4-18
Figure 4-2.3B . . Chronic Hepatitis B Serology 4-18
Figure 4-3.3 . . . Life Cycle of DNA Virus. 4-21
Figure 4-3.4 . . . Koilocytotic Atypia on a Pap Smear 4-22

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Table of Contents

Microbiology Figures

Figure 4-3.5A . . HSV-1 Gingivostomatitis 4-25
Figure 4-3.5B . . HSV-2 Genital Lesions 4-25
Figure 4-3.5C . . Tzank Smear 4-26
Figure 4-3.5D . . Chickenpox Rash 4-26
Figure 4-3.5E . . Zoster/Shingles Rash 4-27
Figure 4-3.5F . . Hairy Oral Leukoplakia 4-27
Figure 4-3.5G . . Burkitt Lymphoma 4-27
Figure 4-3.5H . . Serologic Test Results for Epstein-Barr Virus 4-28
Figure 4-3.5I. . . Owl's Eye Inclusion Body 4-29
Figure 4-3.5J. . . CMV Retinitis. 4-29
Figure 4-3.5K . . Smallpox Rash. 4-31
Figure 4-3.5L . . Molluscum Contagiosum Virus 4-31
Figure 4-4.3 . . . Life Cycle of ss(+)RNA Viruses 4-33
Figure 4-4.4A . . Skin Rash of Hand-Foot-and-Mouth Disease 4-34
Figure 4-4.4B . . Oral Exanthem of Hand-Foot-and-Mouth Disease 4-34
Figure 4-4.5A&B Rubella Rash: Day 1 (*left*) and Day 3 (*right*) 4-37
Figure 4-4.5C . . Congenital Rubella Cataracts. 4-37
Figure 4-4.5D . . Congenital Rubella Microcephaly 4-37
Figure 4-4.5E . . Anatomy of HIV. 4-39
Figure 4-4.5F . . HIV Genome 4-40
Figure 4-4.5G . . HIV Life Cycle 4-41
Figure 4-4.5H . . The Global Effects of HIV Infection on the Immune Response . . 4-42
Figure 4-4.5I. . . Kaposi Sarcoma, Skin Lesions 4-43
Figure 4-4.5J. . . Kaposi Sarcoma, Microscopic. 4-43
Figure 4-4.5K . . Toxoplasmosis Ring-Enhancing Lesions in AIDS 4-44
Figure 4-5.1 . . . Life Cycle of ss(-)RNA Viruses 4-46
Figure 4-5.4A . . Rabies Virus 4-47
Figure 4-5.4B . . Electron Micrograph of Measles Virus 4-48
Figure 4-5.4C . . Koplik Spots 4-48
Figure 4-5.4D . . The Measles Rash 4-48
Figure 4-5.4E . . Mumps-Associated Parotitis. 4-49
Figure 4-5.5A . . Anatomy of Influenza Virus. 4-53
Figure 4-5.5B . . Electron Micrograph of Influenza Virus 4-53

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Table of Contents

Microbiology Figures

Chapter 5 Mycology

Figure 5-1.1 . . . Anatomy of Yeast Cell. 5-1
Figure 5-1.4 . . . Yeast 5-2
Figure 5-1.6 . . . Action of Antifungal Agents 5-4
Figure 5-2.1A . . KOH Preparation of *Malassezia* Skin Scraping 5-5
Figure 5-2.1B . . Pityriasis Versicolor 5-5
Figure 5-2.2A . . Tinea Capitis 5-6
Figure 5-2.2B . . Tinea Corporis 5-6
Figure 5-2.2C . . Tinea Cruris 5-6
Figure 5-2.2D . . Tinea Unguium 5-6
Figure 5-2.3A . . Infectious Form of *Sporothrix schenckii* 5-7
Figure 5-2.3B . . Rose Gardener's Disease 5-7
Figure 5-3.0 . . . Geographic Distribution of Systemic Mycoses in the U.S. 5-8
Figure 5-3.1A . . Dissemination of *Blastomyces* to the Skin 5-8
Figure 5-3.1B . . *Blastomyces* Budding Yeast 5-8
Figure 5-3.2A . . Environmental Form of *Histoplasma capsulatum* 5-9
Figure 5-3.2B . . Tissue Form of *Histoplasma capsulatum* 5-9
Figure 5-3.3A . . *Coccidioides* Spherule. 5-9
Figure 5-3.3B . . Arthroconidia of *Coccidioides*. 5-10
Figure 5-3.4 . . . *Paracoccidioides* Tissue Form 5-10
Figure 5-4.1A . . India Ink Preparation of *Cryptococcus neoformans*. 5-11
Figure 5-4.1B . . *Cryptococcus neoformans* Encapsulated Yeasts in Tissue 5-11
Figure 5-4.2 . . . *Aspergillus* Conidiophores and Conidia 5-11
Figure 5-4.3A . . *Candida albicans*: Thrush 5-12
Figure 5-4.3B . . Germ Tube Test 5-12
Figure 5-4.4A . . Zygomycosis 5-13
Figure 5-4.4B . . Ribbon-Like Hyphae of Zygomycophyta 5-13
Figure 5-4.5 . . . *Pneumocystis* Honeycomb Exudate 5-13

Chapter 6 Parasitology

Figure 6-2.2A . . *Plasmodium* Life Cycle 6-4
Figure 6-2.2B . . Patterns of Malarial Fevers 6-5

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Table of Contents

Microbiology Tables

Chapter 1 Microbial Pathophysiology

Table 1-1.0 Infectious Agents 1-1
Table 1-2.0 Normal Flora 1-2
Table 1-3.1 Microbial Adherence 1-3
Table 1-3.5 Hypersensitivities. 1-6
Table 1-3.6 Exotoxins 1-8

Chapter 2 Bacterial Genetics and Drug Resistance

Table 2-4.3 Mechanisms of Genetic Exchange 2-17
Table 2-5.3 Mechanisms of Resistance Transfer 2-23

Chapter 3 Bacteriology

Table 3-1.1 Bacterial Structure and Morphology 3-3
Table 3-2.1 Special Bacterial Growth Requirements 3-5
Table 3-2.2 Bacterial Oxygen Requirements 3-6
Table 3-3.1A Commonly Tested Media 3-7
Table 3-3.1B Gram Stain 3-8
Table 3-3.1C Acid-Fast Stain 3-8
Table 3-5.1 Clinical Syndromes of *S. aureus* 3-11
Table 3-5.2A Pathogenic Features of *S. pyogenes* 3-14
Table 3-5.2B Acute Suppurative Infections of S. pyogenes. 3-15
Table 3-5.2C Non-suppurative Sequelae of *S. pyogenes* 3-16
Table 3-5.2D Clinical Syndromes/Diagnosis/Treatment of *S. pneumoniae* 3-17
Table 3-6.0 Gram-Positive Rods 3-19
Table 3-6.1A Tetanus Wound Management. 3-21
Table 3-6.1B *C. botulinum* Clinical Syndromes 3-22
Table 3-6.4A *M. leprae* Clinical Syndromes. 3-29
Table 3-6.4B Atypical Mycobacterial Characteristics 3-30
Table 3-7.1 Gram-Negative Cocci: Species Differentiation 3-31
Table 3-8.1 Other *Vibrio* Species. 3-41
Table 3-8.2 Pathogenic Features of *Escherichia*. 3-45
Table 3-9.2 Syphilis: Clinical Syndromes 3-53
Table 3-9.3 Lyme Disease (Borreliosis): Clinical Syndromes 3-54
Table 3-10.0 Unusual Bacteria 3-56

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Microbiology Tables

Table 3-10.2A Rickettsiae Species 3-58
Table 3-10.2B *Ehrlichia* Species 3-59

Chapter 4 Virology

Table 4-1.2 Viral Genomic Replication 4-7
Table 4-1.5 Viral Oncogenesis 4-13
Table 4-2.1 Overview of Hepatotropic Viruses 4-16
Table 4-2.3 Serologic Diagnosis of Hepatitis 4-19
Table 4-3.2 DNA Virus Families 4-20
Table 4-3.5 Summary of Herpesvirus Infections 4-30
Table 4-4.2 Positive-Sense RNA Viruses 4-32
Table 4-4.5A HIV Genes 4-40
Table 4-4.5B CDC Staging of HIV Infection 4-44
Table 4-4.5C HIV Therapies 4-45
Table 4-4.5D CDC Recommendations for Standard Prophylaxis 4-45
Table 4-5.3 ss(-)RNA Viral Families 4-47
Table 4-5.5A Arenaviruses 4-52
Table 4-5.5B Bunyaviruses 4-52
Table 4-6.1 Characteristics of Double-Stranded RNA Viruses 4-55
Table 4-6.2 Reoviruses 4-55
Table 4-7.1 Prion Diseases in Humans 4-56

Chapter 5 Mycology

Table 5-4.3 *Candida albicans*: Clinical Syndromes 5-12

Chapter 6 Parasitology

Table 6-1.1 Protozoan Parasites 6-1
Table 6-1.2 Metazoan Parasites 6-2
Table 6-1.4 Antiparasitic Drugs 6-2
Table 6-2.1 Mucosal Protozoa 6-3
Table 6-2.2A Diagnosis of *Plasmodium* Species 6-6
Table 6-2.2B Blood and Tissue Protozoa 6-7
Table 6-3.1 Nematodes 6-9
Table 6-3.2 Cestodes 6-12
Table 6-3.3 Trematodes 6-13

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Immunology

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1 Components of the Immune System

The *immune system* is a complex set of specialized cells and proteins dedicated to identifying and destroying foreign invaders and altered host cells.

1.1 Innate Immune System

The immune system's first line of defense against invading pathogens is a set of barriers: cellular, anatomical, and chemical. Collectively referred to as the *innate immune defenses*, these barriers have:

- **No specificity:** They produce the same response to a wide variety of stimuli.
- **No regulatory control:** They act reflexively, with or without regulation by other cells.
- **No memory:** Their performance is not improved by previous stimulation.
- **Limited diversity:** They have a limited repertoire of functions.

1.2 Acquired Immune System

Once innate barriers have been breached, the immune system's second line of defense is activated. *Acquired* (or *adaptive*) *immunity*, as this second line of defense is called, consists of lymphocytes and antigen-presenting cells. In contrast with the innate immune defenses, acquired immune responses have:

- **Specificity:** They produce a specific response to specific stimuli.
- **Regulatory control:** Their response to stimuli is tightly regulated.
- **Immunologic memory:** Previous stimulation improves their performance.
- **High diversity:** They possess a wide variety of specificities.

USMLE® Key Concepts

For Step 1, you must be able to:

- Identify the components of innate and adaptive immune responses.
- Explain the functions of innate and adaptive immune responses.
- Describe the interrelationships between innate and adaptive immunity.

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▼**Table 1–1.2** Components and Characteristics of the Immune System

Components	Innate	Acquired
Anatomic and chemical	Skin, mucosa, chemicals, temperature, pH	Lymph nodes, spleen, mucosal-associated lymphoid tissues
Serum proteins	Complement	Antibodies
Cells	Phagocytes and natural killer (NK) lymphocytes	Lymphocytes other than NK cells
Characteristics		
Specificity	For shared microbial structures	For specific *epitopes** of foreign agents
Regulatory control	No	Yes
Memory	No	Yes
Diversity	Limited	High

*An *epitope* is the component of the antigen that is complementary to the idiotype of the cellular receptor.

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2 The Design of the Immune System

Although historically it was popular to divide innate and acquired immunity into separate systems, it is clear that they work together as an orchestrated whole in the protection of the body from disease. While innate immunity responds to foreign invaders first, it does not operate in a vacuum. Instead, it receives important amplifying signals from acquired immunity through the following:

- The cytokines of innate phagocytes are necessary for the activation of T lymphocytes (the "generals" of the acquired immunologic "army").
- The cytokines of T lymphocytes stimulate phagocytes to become "angry phagocytes" which are more effective at phagocytosis and intracellular killing.
- The products of differentiated B lymphocytes, antibodies, increase the speed with which phagocytes engulf *foreign invaders* via a process known as *opsonization*.
- Antibodies secreted by plasma cells activate complement (a serum protein) to enhance phagocytosis and attract inflammatory cells.

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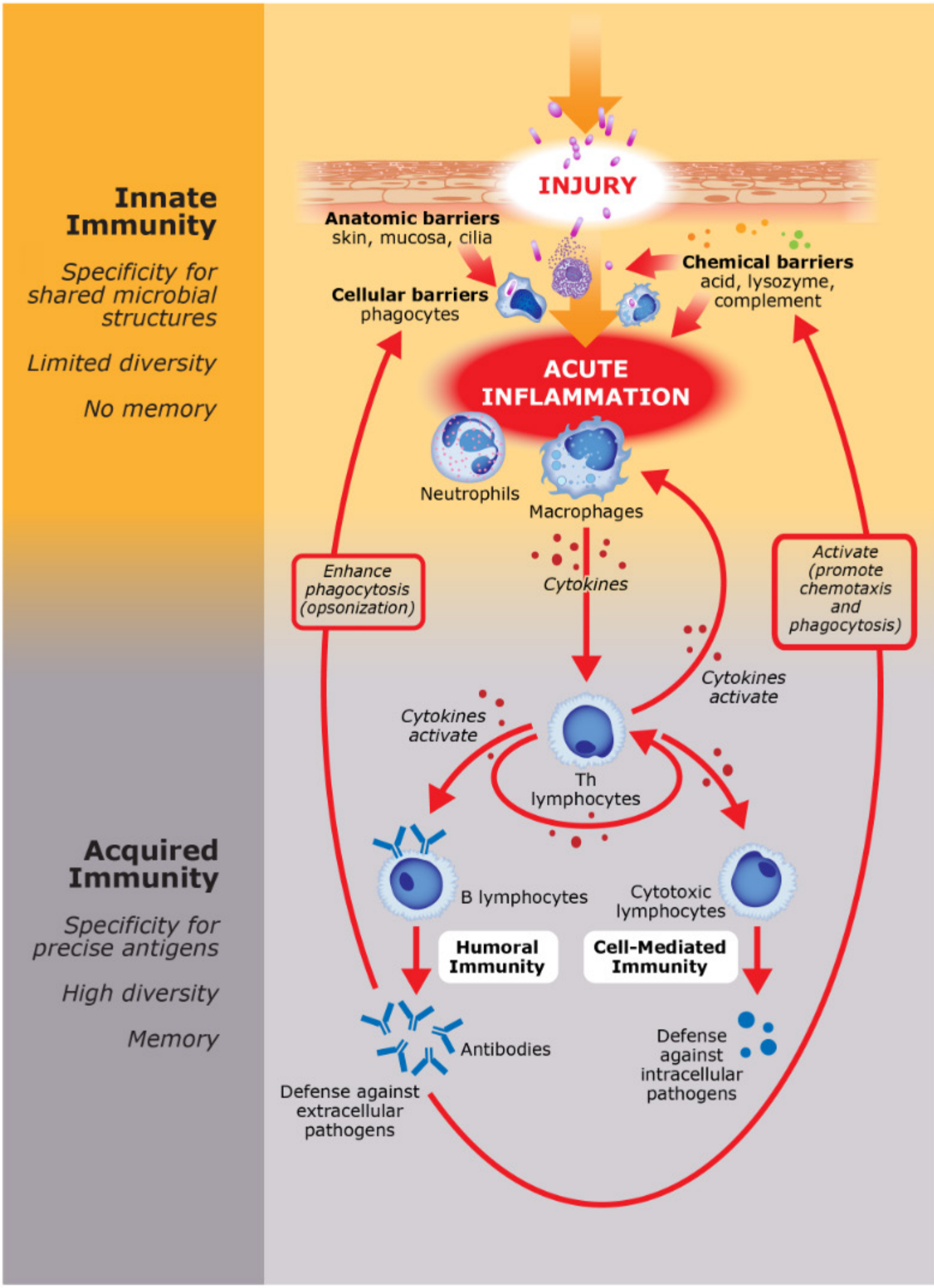

▲ **Figure 1–2.0** Overview of the Immune System

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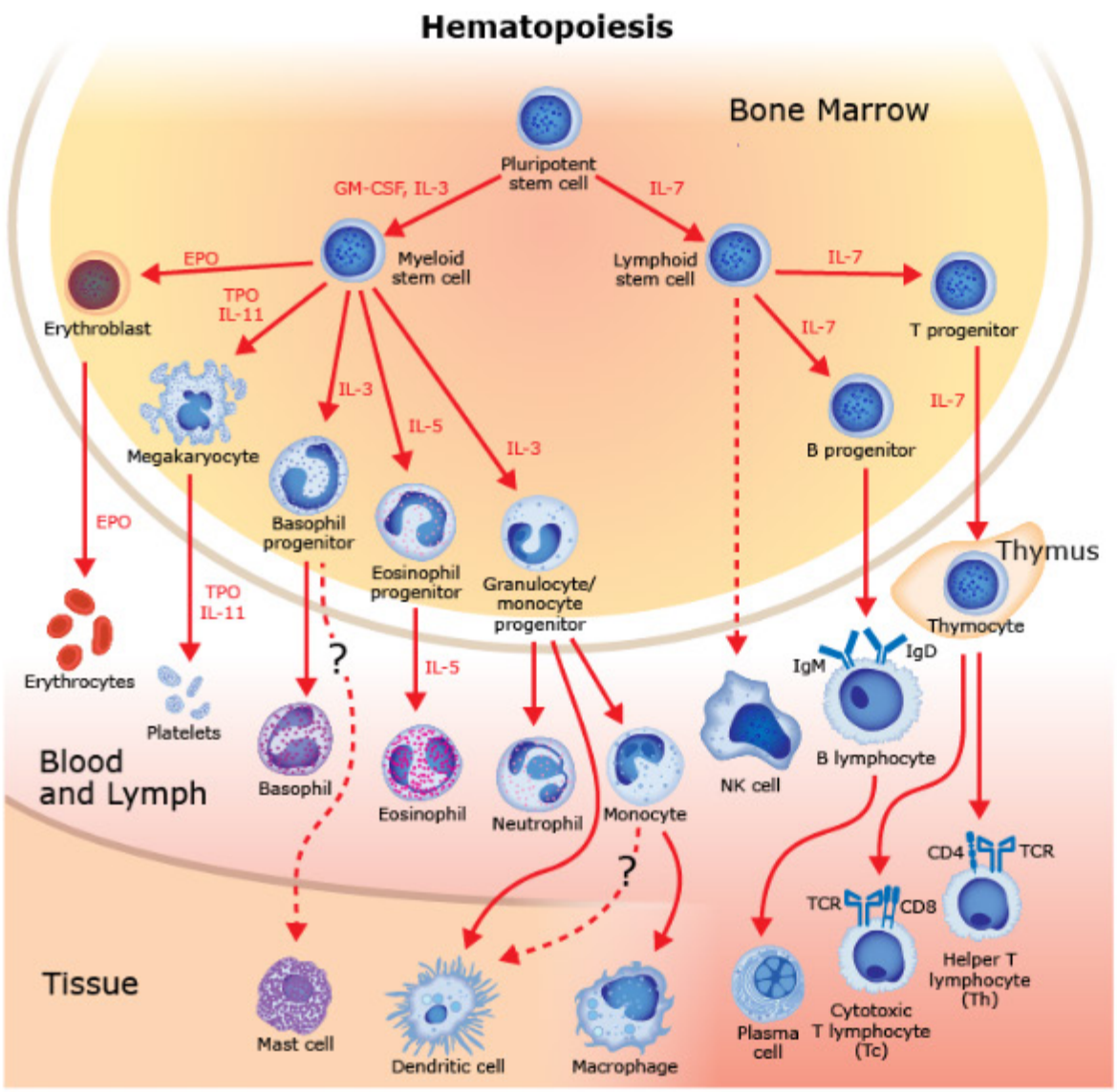
1 Origin of Immune Cells

The cells of the immune system originate in the bone marrow in a process referred to as *hematopoiesis*. In the bone marrow, a pluripotent stem cell differentiates down one of two lineages in the presence of specific *cytokines* or soluble mediators:

- **Common Myeloid Progenitor:** Created in the presence of granulocyte-monocyte colony stimulating factor (GM-CSF) or *interleukin-3 (IL-3)*. This cell is the originator of erythrocytes, platelets, granulocytes (neutrophils, basophils, and eosinophils), monocytes, macrophages, and dendritic cells.
- **Common Lymphoid Progenitor:** Created in the presence of *interleukin-7 (IL-7)*. This cell ultimately differentiates into B lymphocytes, T lymphocytes, or natural killer (NK) cells. The T lymphocyte precursor leaves the bone marrow and migrates to the second primary lymphoid organ, the *thymus*, to undergo further differentiation into *helper T cells (Th)* or *cytotoxic T cells (Tc)*.



▲ **Figure 2–1.0** Bone Marrow Origin of Immune Cells

USMLE® Key Concepts

For Step 1, you must be able to:

- Identify the origin, distribution, and function of immune cells.
- Explain how B and T lymphocytes recognize foreign substances.
- Describe how gene segment rearrangement produces the diversity of cell receptors.
- Explain how tolerance of self is established in the primary lymphoid organs.

Memory Aid

Turn the bone marrow cytokine numbers in a new orientation and they tell you what they do:

IL-**3** → **m** (for myeloid)

IL-**7** → **L** (for lymphoid)

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2 The Cells of the Immune System

▼Table 2–2.0A Myeloid-Origin Cells

Image	Name	Identification	Location	Function
		IN THE CIRCULATION		
	Neutrophil (polymorphonuclear leukocyte or PMN)	Multilobed nucleus and small pink cytoplasmic granules	Blood, 1,800–7,800/μL	Phagocytosis, microbicidal to extracellular organisms, abscess formation
	Eosinophil	Bilobed nucleus, large pink cytoplasmic granules	Blood, 0–450/μL (increase in allergic and anthelminthic responses)	Kill antibody-coated helminths by releasing major basic protein
	Basophil	Bilobed nucleus, large purple cytoplasmic granules, Fcε receptor	Blood, 0–200/μL	Non-phagocytic, release pharmacologically active substances during allergic reactions and helminth invasion, differentiate into mast cells in the epithelium and submucosa
	Monocyte	Large, indented, non-lobed nucleus, CD4+, CD16+, and **CD14+**	Blood, 0-900/μL	Phagocytic, leave blood to become tissue macrophages
		IN THE TISSUES		
	Macrophage (Histiocyte, Langerhans cell, Kupffer cell, osteoclast, mesangial cell, microglia)	Ruffled membrane, cytoplasm filled with vesicles and vacuoles, CD4+, CD16+, and **CD14+**	Tissues	Phagocytosis, secretion of cytokines, antigen presentation
	Dendritic cell	Long cytoplasmic arms	Epithelium and submucosa	Phagocytosis, antigen capture, presentation and transport
	Mast cell	Small nucleus, large numbers of large purple granules	Tissues	End cell of basophil lineage, releases pharmacologically active substances locally during allergic responses or helminthic invasion

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Clinical Application

When a patient develops a normocellular *granulocytosis* (increase in the number of normal circulating granulocytes), this reflects an infection with some sort of extracellular pathogen. The presence of a high count of immature PMNs (band forms; *left shift*) typically indicates bacterial infection. When a patient has a *mononucleosis* (increase in the number of circulating monocytes and lymphocytes), this reflects infection with an intracellular pathogen such as a virus.

Clinical Application

CD14 is another name for the *endotoxin receptor*. It binds to bacterial lipopolysaccharide and starts the clinical process of endotoxin shock by stimulating oversecretion of monocyte/macrophage cytokines, which can become life-threatening in high doses. CD16 is another name for the receptor for the tail (Fc region) of the immunoglobulin G (IgG) molecule. It also is present on neutrophils, NK cells, eosinophils, and dendritic cells. CD16 also is known as FcRγ.

Important Concept

- Know the numbered cytokines! The named cytokines, such as GM-CSF, thrombopoietin, or erythropoietin, in which the name reveals the function, are rarely tested!
- Therapy for patients with bone marrow dyscrasias or chemotherapeutic bone marrow damage is now possible with the availability of hematopoietic or lymphopoietic cytokines made by recombinant DNA technology.

▼Table 2–2.0B Lymphoid Origin Cells

Image	Name	Identification	Location	Function
IN THE CIRCULATION				
	B cell	Large dense nucleus almost fills the cell, small rim of agranular cytoplasm, CD19–21+	Blood, 1,000–4,000/µL	Differentiate into plasma cells and produce antibodies
	T helper (Th) cell	CD3+, CD4+		Regulate immune responses
	Cytotoxic T (Tc) cell	CD3+, CD8+		Kill altered cells
	Natural killer (NK) cell	CD16+, CD56+		Kill altered cells that lack "self" molecules
IN THE TISSUES				
	Plasma cell	Small dark nucleus, prominent Golgi apparatus	Lymph nodes, bone marrow, spleen, mucosal associated lymphoid tissue (MALT)	Production of one specific antibody for two-week life span

Photo Credits: (top) Dr. John D. Cunningham/Visuals Unlimited, Inc.; (bottom) Biophoto Associates/Science Source

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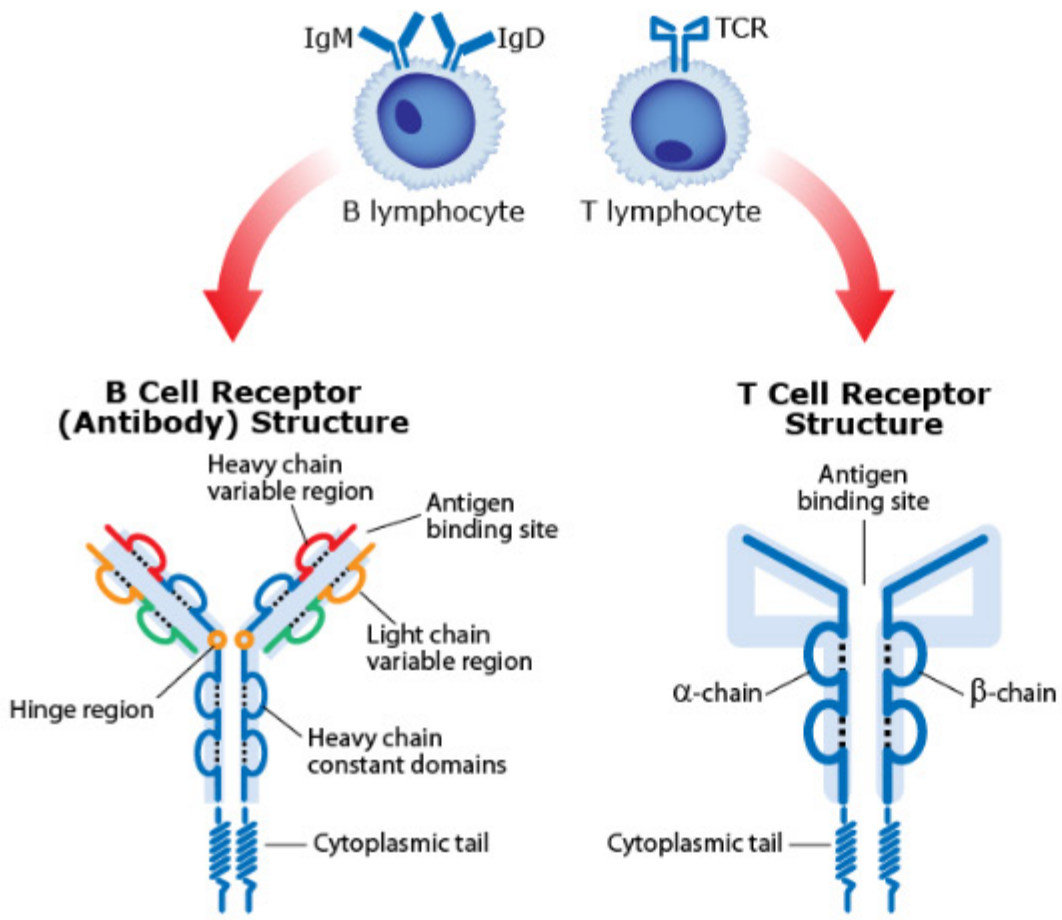
3 Development of Antigen Recognition Molecules

An *antigen* (from "*anti*body *gen*erator") is a foreign substance that can bind to a lymphocyte antigen receptor. It is distinct from an *immunogen* (from *immun*ity *gen*erator), which is a foreign substance with enough size and molecular complexity to generate an immune response.

B and T lymphocytes possess antigen recognition molecules on their surfaces that allow them to respond specifically to the small molecular details of a foreign substance. These antigen recognition molecules are members of the *immunoglobulin superfamily of genes*, encoding soluble or cell surface proteins that are involved in cell recognition, binding, and adhesion abilities.

- The antigen receptor of the mature, naive B lymphocyte (BCR) consists of the molecules IgM and IgD, which are membrane-bound and possess an intracytoplasmic tail required for signal transduction. BCRs are capable of binding unprocessed antigens of virtually any chemical composition.
- The antigen receptor of the mature, naive T lymphocyte consists of a related structure referred to as the T cell receptor (TCR). TCRs are able to recognize only peptides found on the surface of specialized antigen-presenting cells (APCs).



▲ **Figure 2–3.0** Antigen Receptors of B and T Lymphocytes

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3.1 Structure of the BCR

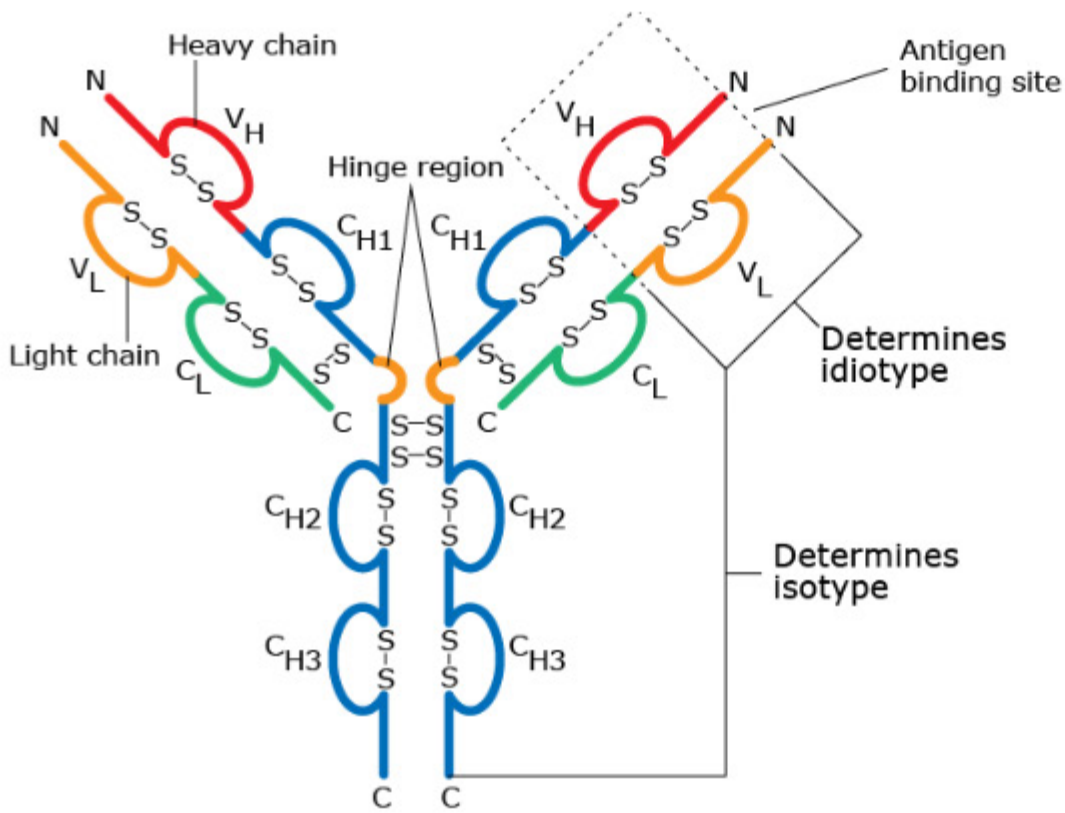
The BCR is the predecessor of serum Ig. Its basic monomeric structure consists of two heavy chains and two light chains, with reference to their relative molecular weight and amino acid chain length. The two *heavy chains* and the two *light chains* for a given B cell are identical to one another. As a result, two identical, unique three-dimensional antigen recognition pockets *(idiotypes)* are formed by the extremely variable amino acid configurations of each N-terminal arm *(variable domains)*. Thus, each monomeric BCR is said to have a *valence* of two.

Downstream toward the carboxy terminus of each amino acid chain are found *constant domains* that vary between classes *(isotypes)* of molecules. The isotypes of heavy chains are named with the Greek letter for the corresponding immunoglobulin produced:

- Two mu (μ) heavy chains make up IgM
- Two delta (δ) heavy chains make up IgD
- Two gamma (γ) heavy chains make up IgG
- Two alpha (α) heavy chains make up IgA
- Two epsilon (ε) heavy chains make up IgE

The isotypes of the light chains are referred to as kappa (κ) or lambda (λ), and each monomer of BCR will have two identical chains produced by that cell and all of its descendants for life. The heavy chains are held together with a *"hinge region"* of chemical bonds that allow some flexibility of movement between the two antigen-binding arms.

On the cell membrane next to each BCR is a *signal transduction complex*. This is a multichain structure composed of two immunoglobulin-related molecules (Ig-α and Ig-β) and two other molecules known as *cluster of differentiation (CD) 19 and 21*. When a B lymphocyte binds to its appropriate antigen, this complex begins a cascade of intracytoplasmic phosphorylation events that activate and clone the cell.



▲ **Figure 2–3.1** Structure of Immunoglobulin (BCR)

Connection to Microbiology

Epstein-Barr virus (the agent of heterophile-positive mononucleosis) uses CD21 as its receptor to infect B lymphocytes. The resulting polyclonal activation of B lymphocytes causes the lymphadenopathy, splenomegaly, and production of heterophilic antibodies characteristic of the disease.

Clinical Application

Because all lymphocytes have a signal transduction complex, the measurement of numbers of cells wearing CD19 and CD21 is used clinically to count the number of B cells in a patient. The number of CD3+ cells is taken to represent the total number of T lymphocytes.

Clinical Application

Bence Jones proteins are free immunoglobulin light chains found in the serum or urine of patients with multiple myeloma or Waldenström macroglobulinemia. They are generally kappa light chains, reflecting the overall 2:1 production ratio of kappa to lambda chains in humans.

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Clinical Application

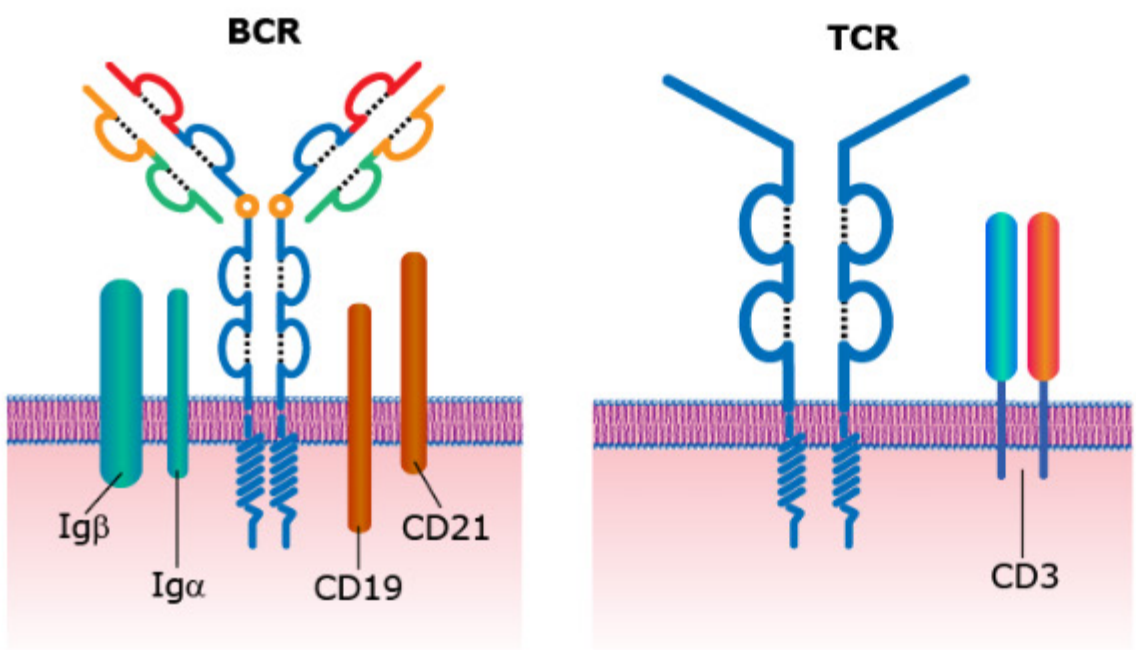
Both heavy and light chains also possess *allotypes*, or allotypic markers. These are genetic polymorphisms that affect amino acid sequences in the constant domains of the heavy and light chains, but have no effect on the function of the molecule. Because these amino acid "fingerprints" are inherited from parents, these markers constitute the one "marker" of genetic lineage concerning immunoglobulins that could be used to "rule out" candidates in cases of questionable paternity. However, much more sophisticated and accurate determinations are used today.

3.2 Structure of the T Cell Antigen Receptor (TCR)

The TCR consists of two amino acid chains referred to as *alpha* and *beta*. The chains do not differ enough in weight and length to be referred to as heavy and light, but there are analogies. As with the BCR, on the N-terminus of each chain, a highly variable amino acid domain is present, and the groove between these two variable domains ultimately binds peptides presented by APCs.

Downstream toward the carboxy terminus of each chain are constant domains that make up the isotype of the molecule. In humans, 95% of all circulating T lymphocytes express the alpha-beta isotype. A very small proportion of T lymphocytes that populate the intestinal mucosa possess a gamma-delta isotype, but their role in the immune response is not well understood.

The signal transduction complex in the T cell is a multichain structure known collectively as CD3, and this molecule, the *"pan T cell marker,"* is used in clinical medicine to count the number of T cells in a patient.



▲ **Figure 2–3.2** B and T Cell Signal Transduction Complexes

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▼ **Table 2–3.2** Comparison of B and T Cell Antigen Receptors

Characteristic	BCR	TCR
Idiotypes per cell	One	One
Isotypes per cell	Two (IgM and IgD)	One (α/β or γ/δ)
Valence per molecule	Two	One
Flexibility	Yes (hinge)	No
Secretion	Yes	No
Signal transduction	Igα, Igβ, CD19, CD21	CD3

3.3 Gene Rearrangement to Produce Idiotype Diversity

The variable domains of both BCR and TCR are created by a unique process of rearrangement of gene segments in germline DNA lymphocytes developing in the *primary lymphoid organs* (bone marrow and thymus). This "shuffling" of gene segments is what creates the unique amino acid sequence of the N-terminal, approximately 110 amino acids that make up the variable domains of heavy, light, beta, or alpha chains. The shuffling process:

- Permits the generation of the diversity of idiotypes necessary to defend the individual against the millions of different antigens in the environment.
- Is referred to as *VDJ rearrangement* because the names of the gene segments are V (variable), D (diversity), and J (joining).
- Is controlled by the action of the *RAG genes* (recombination activating genes), which are active in extremely primitive lymphoid precursor cells.

An enzyme known as *terminal deoxyribonucleotidyl transferase (Tdt)* is also active during this process, and adds bases into the DNA strand each time V, D, and J segments are spliced, in a random fashion, without a template on the complementary strand. This is referred to as *N-nucleotide addition* (for non-coded nucleotide) and generates even more diversity in the possible idiotypes produced.

The rearrangements are analogous with the BCR heavy chain and the TCR beta chain, and similarly between the BCR light chain and the TCR alpha chain, so only one version is shown. In each lymphocyte, the heavy (or beta) chain rearrangements are undertaken first followed by the light (or alpha) chain rearrangements.

Important Concept

Cells expressing Tdt and *RAG* gene activity are extremely primitive lymphoid cells and should never be found outside of the primary lymphoid organs. Finding them in the circulation is a marker toward the diagnosis of acute lymphoblastic leukemia (ALL).

Memory Aid

To remember the correlation between the chains of BCR and TCR, think of heavy and βig (spelled with a beta) being synonyms. Then, by process of elimination, light and alpha chains must be analogous.

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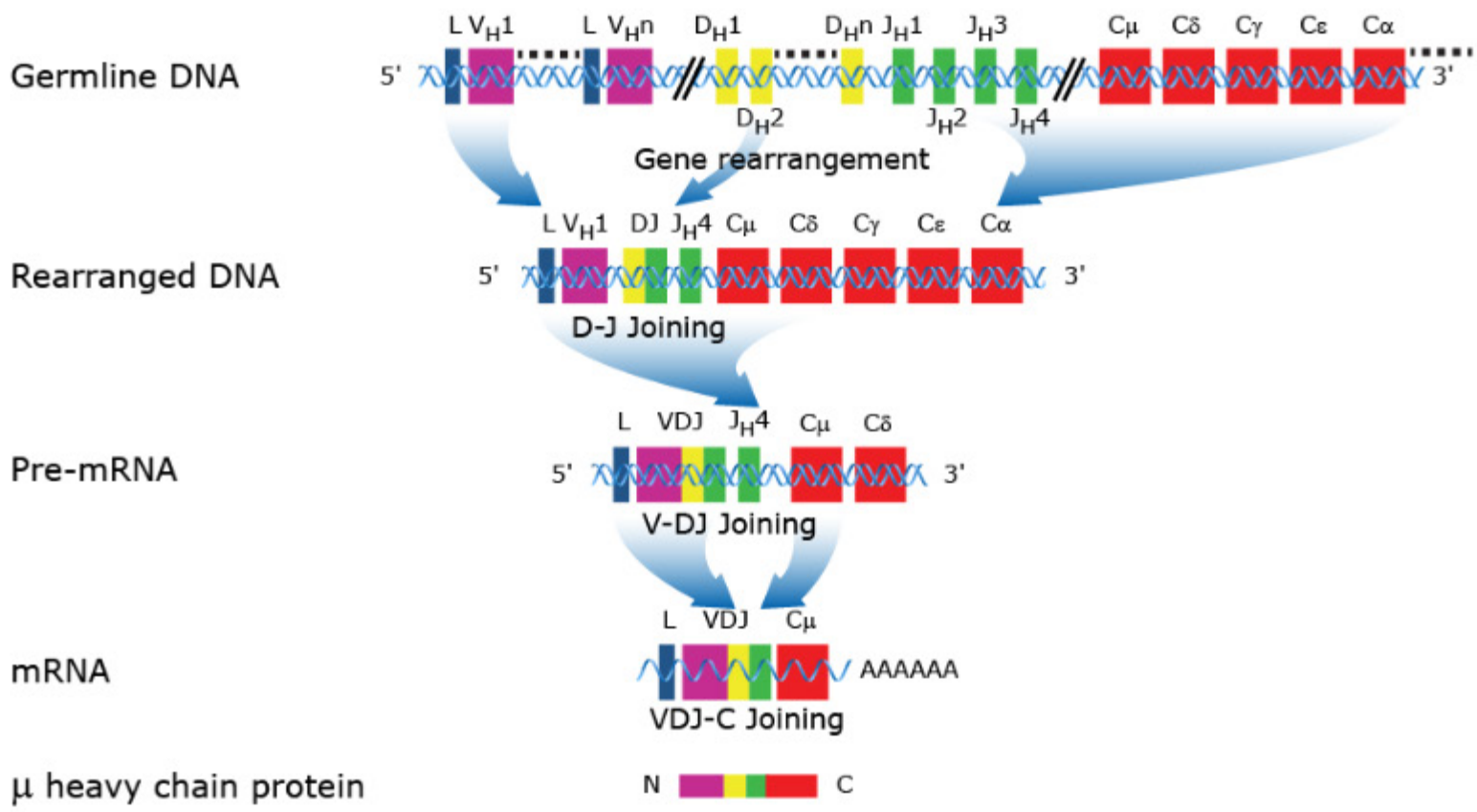
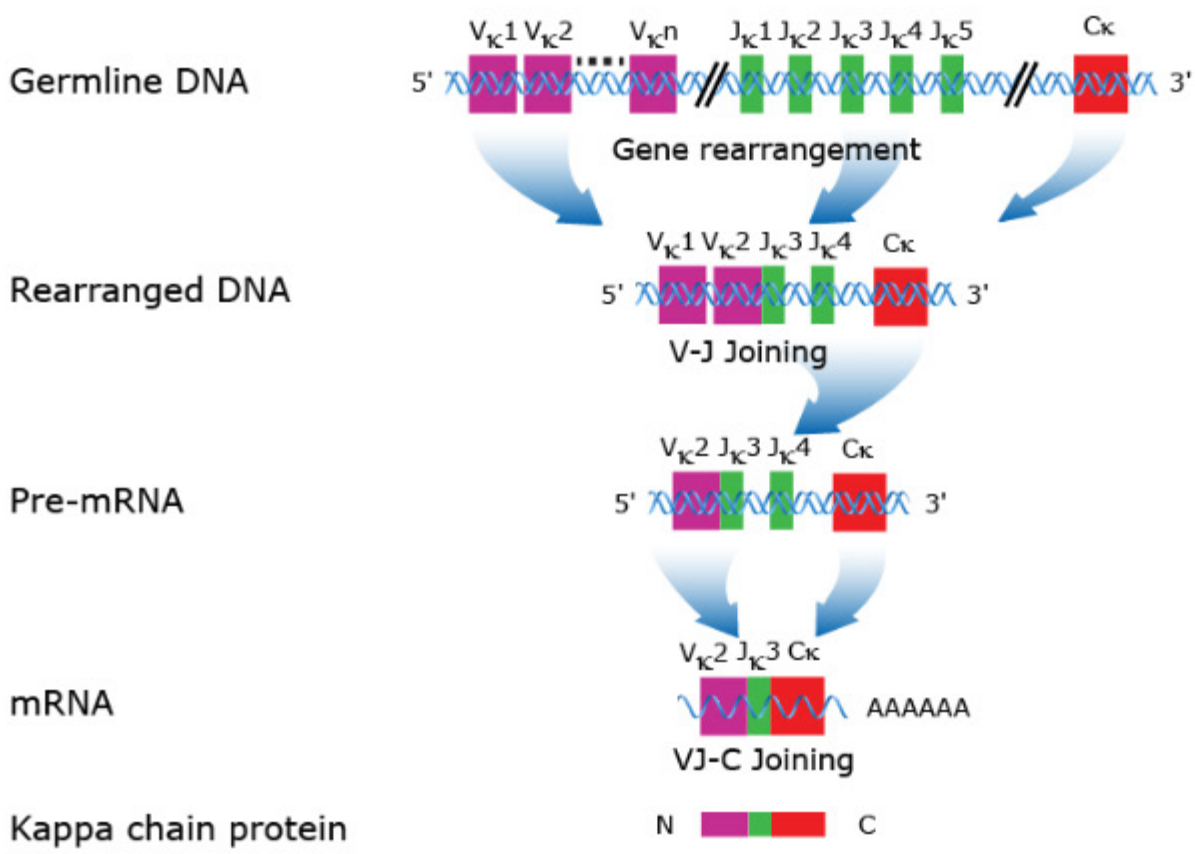
Ig Heavy Chain Synthesis



▲ **Figure 2–3.3A** Heavy Chain Rearrangements

Ig Light Chain Synthesis



▲ **Figure 2–3.3B** Light Chain Rearrangements

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3.4 Allelic Exclusion

Many lymphoid precursors undergoing these complex gene rearrangements create nonfunctional or truncated receptor chains as an accident of the process. Because the cell has two copies of each chromosome, failure to make a functional product with the first chromosome set causes that one to be inactivated, and a second attempt is undertaken with the complementary set. If the attempt at rearrangement is successful with the first chromosome on which it is undertaken, the complementary set is inactivated.

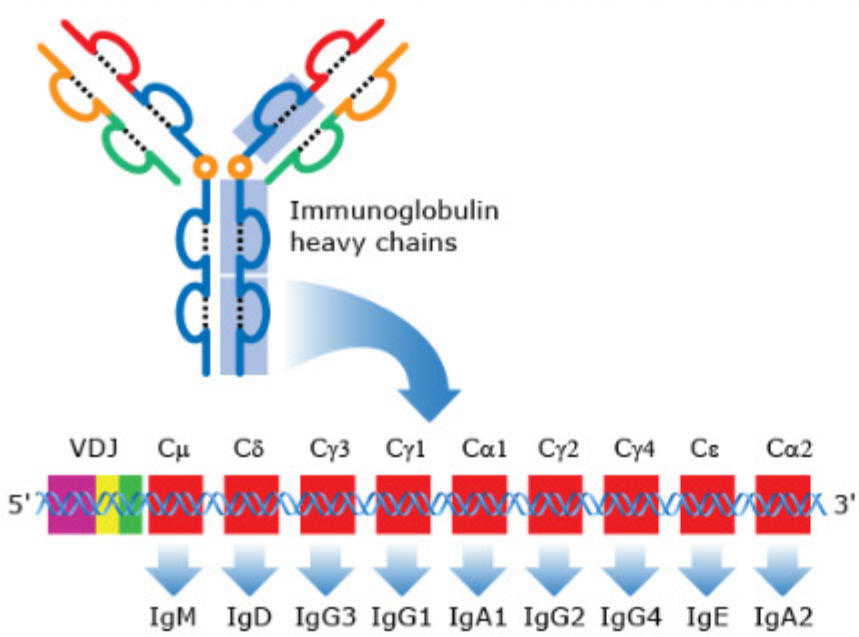
- On each lymphocyte, randomly, only one chromosomal product is expressed, a trait referred to as *allelic exclusion*.
- Because all heavy chain genes are on a single chromosome, and light chain genes are on two separate chromosomes, each cell has two chances to make a functional heavy chain and four chances to make a functional light chain.
- Any lymphocyte that fails on all counts to produce a functional BCR or TCR is induced to undergo apoptosis in the primary lymphoid organs.

▼**Table 2–3.4** B and T Cell Receptor Gene Rearrangements

Mechanism of Diversity	Lymphocytes Involved
VDJ recombination	All except NK cells
N-nucleotide addition	All except NK cells (B cells only heavy chain; T cells both chains)
Combination of two chains	All except NK cells

3.5 Addition of Constant Domains

As the rearranged germline DNA is transcribed, the coding for the constant domains of the BCR and TCR is found downstream from that of the variable domains. In the BCR, the first constant domain downstream is that for μ heavy chains, followed by that for δ heavy chains. These are spliced to the rearranged variable domain coding by *alternative RNA splicing* so that both of these heavy chains (with identical idiotypes) are expressed on each mature naive B cell.



▲**Figure 2–3.5** Germline DNA Sequence in B Cells

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4 Selection of Lymphocyte Receptors

As lymphocyte precursors undertake and achieve these complex, random gene segment rearrangements, it stands to reason that accidentally, some of the cells produced might express a receptor that is "bad" for the organism. Such a receptor would be capable of binding to "self" antigenic determinants and would, if allowed to survive, contribute to the development of autoimmune disease. These lymphocytes are subjected to *clonal deletion* in the primary lymphoid organs.

Connection to Pathology

Understanding the progressive development of lymphocyte markers is important in the staging of lymphoid leukemias. In general, the more primitive the transformed cell, the poorer the prognosis for the patient.

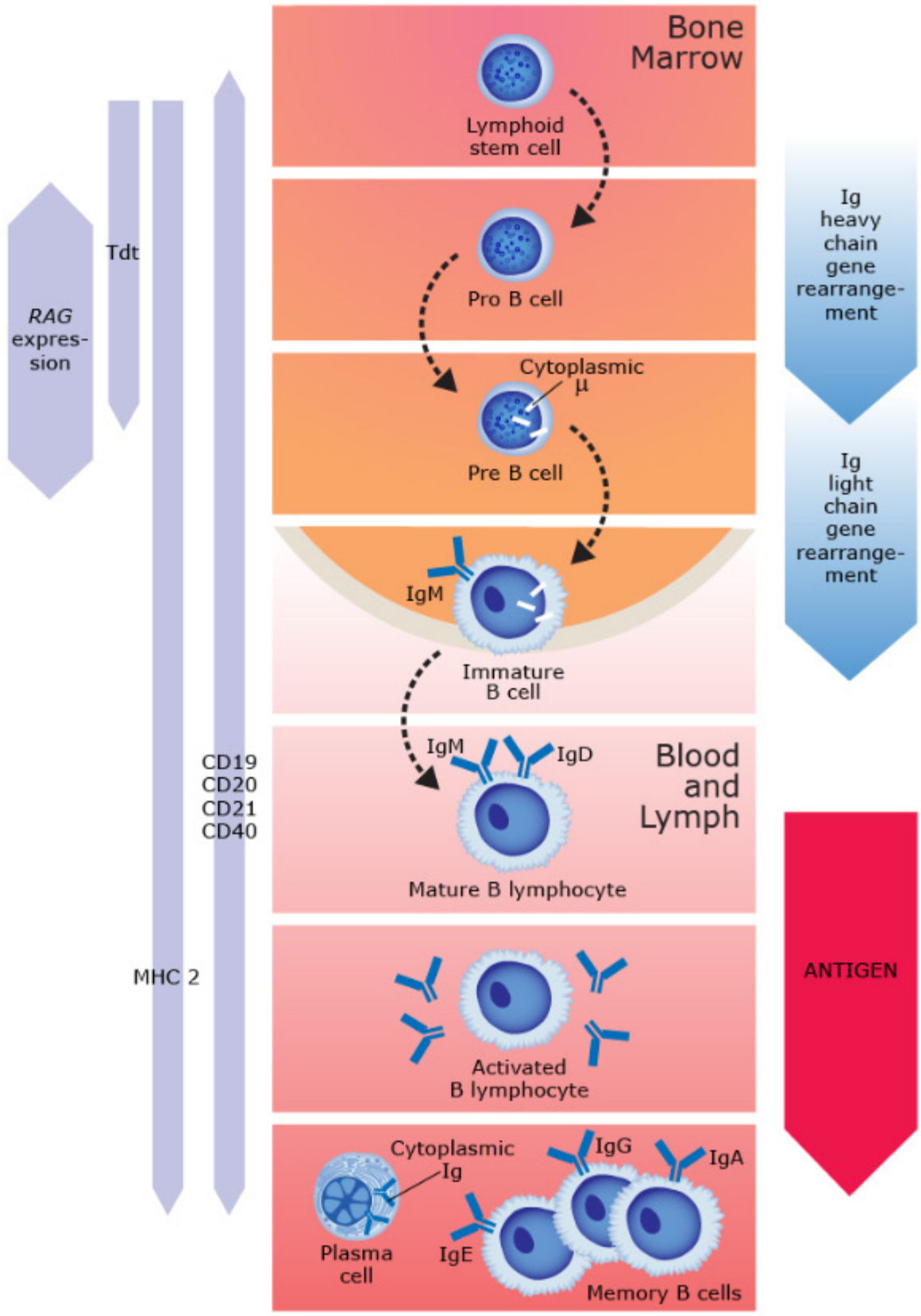
4.1 B Lymphocytes

In the bone marrow, B lymphocytes that produce self-reactive BCRs are induced to undergo apoptosis when they bind too strongly to stromal cells there. This creates *central tolerance* by destroying any cell that might become autoreactive if it were allowed to enter the general circulation. Only cells that have *low affinity* (binding strength) to self molecules in the bone marrow are allowed to progress to the mature, naive B cell stage.

4.2 T Lymphocytes

4.2.1 Thymic Selection

T lymphocyte precursors leave the bone marrow and travel to the thymus, a bilobed primary lymphoid organ above the heart and lungs in the thoracic cavity. The thymus is arranged into an outer cortex and inner medulla, both of which are filled with a network of epithelial cells and antigen presenting cells. Immature thymocytes enter the organ through the vasculature, traversing high endothelial venules and then traveling to the cortex.



▲ **Figure 2–4.1** B Lymphocyte Ontogeny

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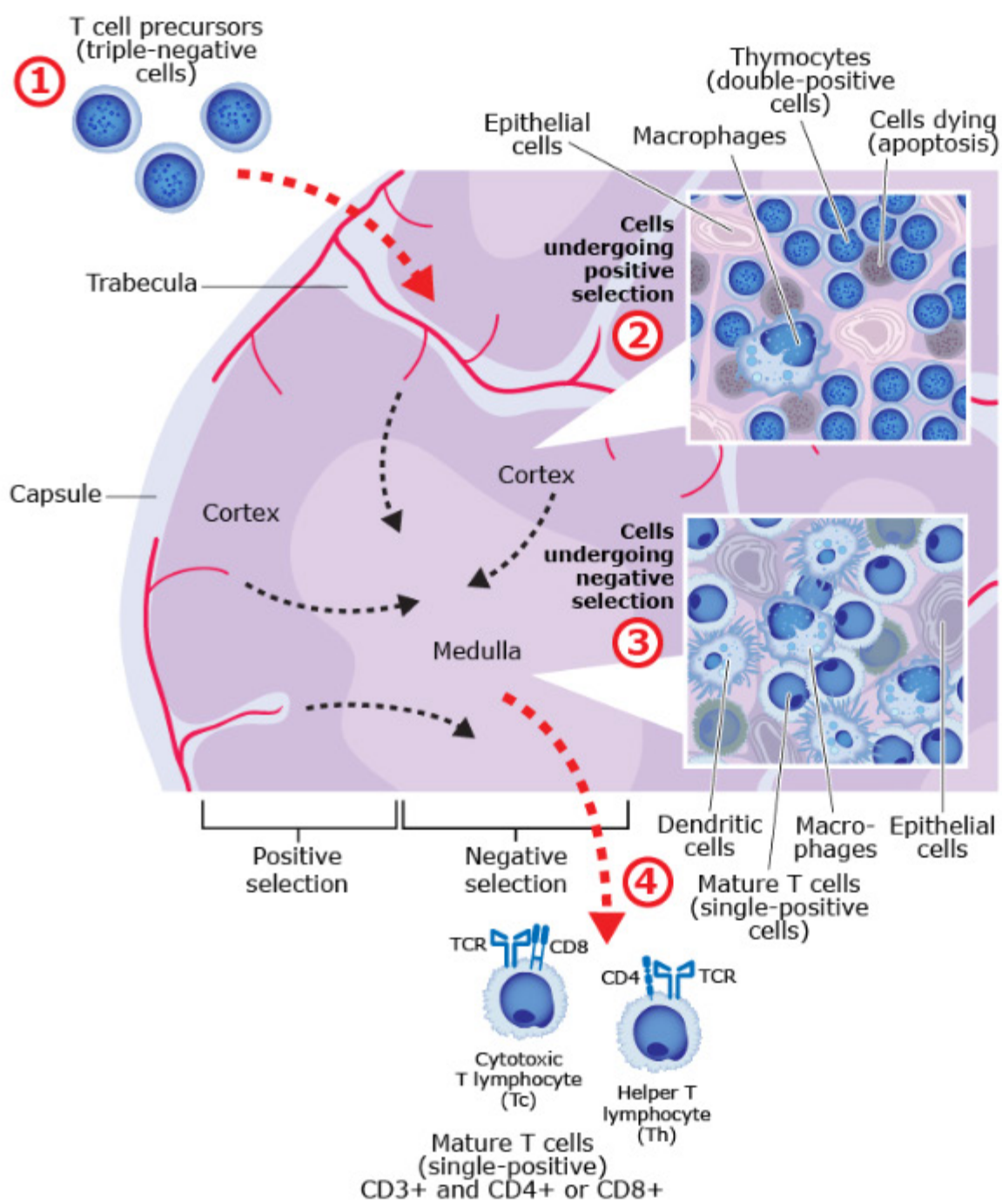
- The cells entering the thymus are said to be *triple-negative cells*—they do not express CD3, CD4, or CD8 markers.
- Epithelial cells in the cortex mediate *positive selection* of thymocytes with TCRs capable of recognizing self antigens referred to as *HLA (human leukocyte antigen) molecules*.
- Cells that have undergone positive selection successfully become *triple-positive cells*: they are CD3+, CD4+, and CD8+. These cells are exposed to dendritic cells in the corticomedullary junction to undergo negative selection.
- In *negative selection*, any cells with excessive affinity for self HLA molecules are forced to undergo apoptosis.

Only a very small proportion of thymocytes entering this organ ever emerge into the lymphatics or circulation as mature, naive T cells that are now CD3+ and either CD4+ or CD8+, and capable of expressing either *helper (Th, CD4+)* or *cytotoxic (Tc, CD8+)* activities in the rest of the body.



▲ **Figure 2–4.2A** Architecture of the Thymus

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4.2.2 Major Histocompatibility Complex (Human Leukocyte Antigens)

The "self" molecules to which developing thymocytes are exposed in the thymus belong to the immunoglobulin superfamily of genes. These molecules are broadly referred to as the *major histocompatibility complex (MHC)*, or specifically within humans, as the *human leukocyte antigens (HLA)*.

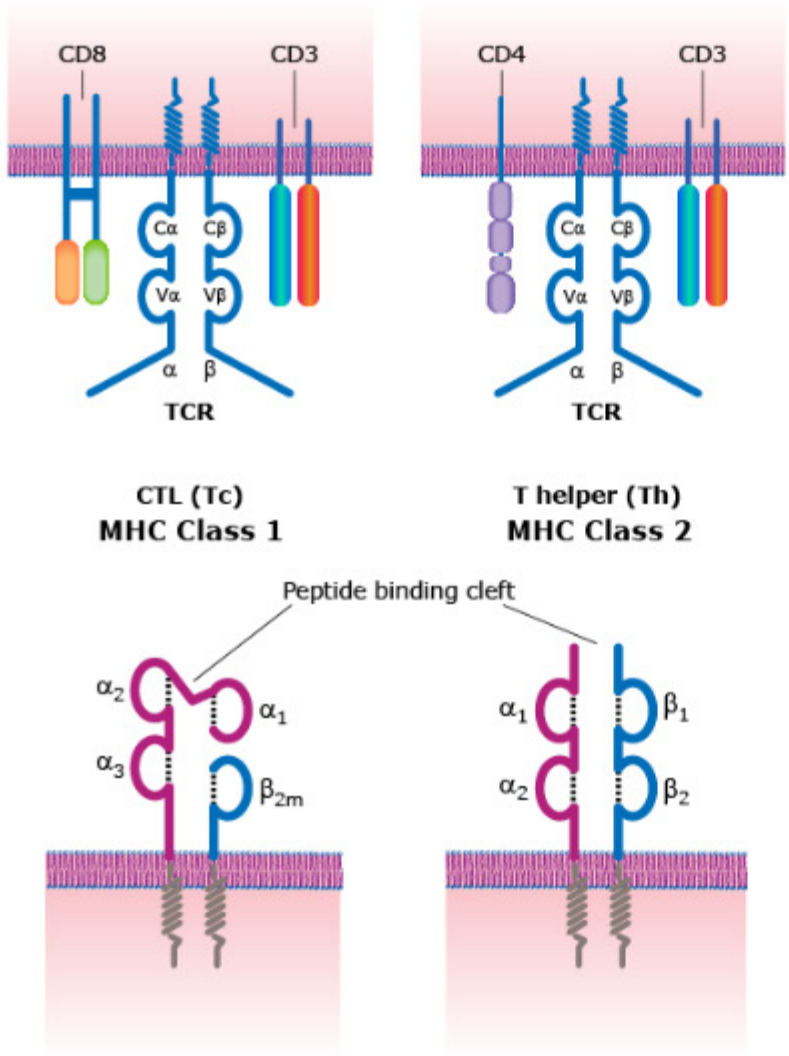
The MHC is the most polymorphic gene system in the human body, and its expression allows the cells of your immune response to distinguish between "self" and invader.

Class 1 MHC

- Found on all *nucleated cells* of the body.
- Expressed *codominantly*, with each cell wearing gene products inherited from both parents.
- On each nucleated cell of the body, there are two copies of *HLA-A*, two of *HLA-B,* and two of *HLA-C* (the class 1 products).

Class 2 MHC

- Found on all *antigen-presenting cells:* B lymphocytes, activated T lymphocytes, monocytes, macrophages, dendritic cells, and activated endothelial cells.
- Expressed codominantly.
- Gene products are known as *HLA-DP, HLA-DQ,* and *HLA-DR.*



▲ **Figure 2–4.2B** Structure and Complementarity of MHC Class 1 and 2

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▼ **Table 2–4.2** Summary of HLA Structure and Expression

	HLA Class 1	HLA Class 2
Gene products	HLA-A, -B, and -C	HLA-DP, -DQ, -DR
Distribution	All nucleated cells	Antigen-presenting cells
Recognition by	Tc (CD8+)	Th (CD4+)
Source of peptides bound	Intracellular	Ingested or endocytosed
Function	Killing of infected or abnormal cells	Presentation of foreign peptides to generate "help"

4.2.3 Details of Positive and Negative Selection

Because the thymus is an *immunoprivileged site*, only normal "self" peptides should be expressed there. The purpose of the positive and negative selection process, then, is to remove any developing thymocytes that could potentially express *autoreactivity* (failure of self-tolerance).

- In the cortex, cells are selected that have some ability to recognize either HLA class 1 or 2 (positive selection).
- Next, cells with too much affinity for these molecules are induced to undergo apoptosis (negative selection).
- As a result, the only cells allowed to leave the thymus and patrol the body for invasion or injury are those capable of cooperating to produce an immune response (CD4+ Th cells) or those capable of recognizing and killing a cell that is altered by intracellular infection or malignant transformation (CD8+ Tc cells).

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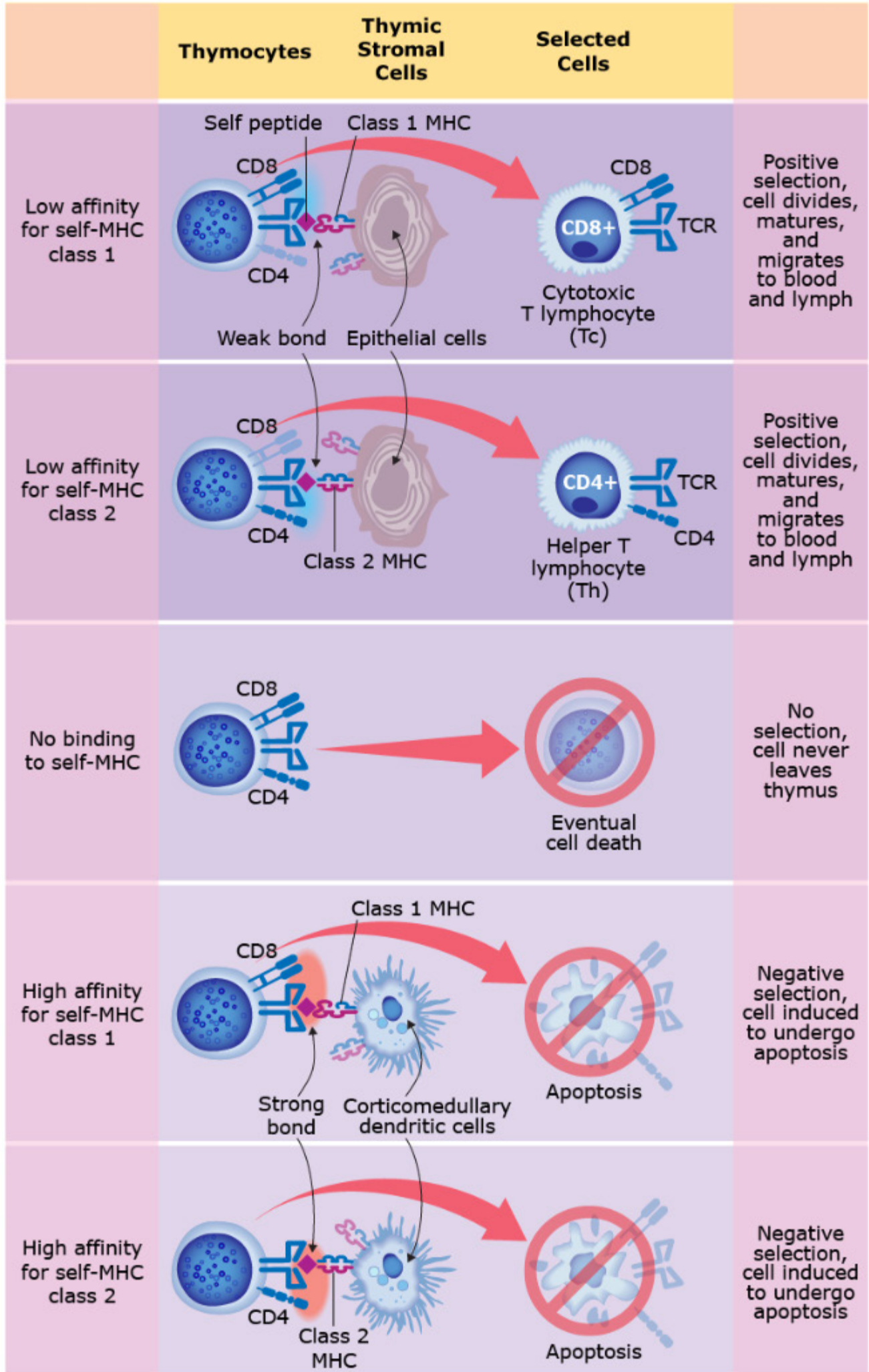

▲ **Figure 2–4.2C** T Cell Selection in the Thymus

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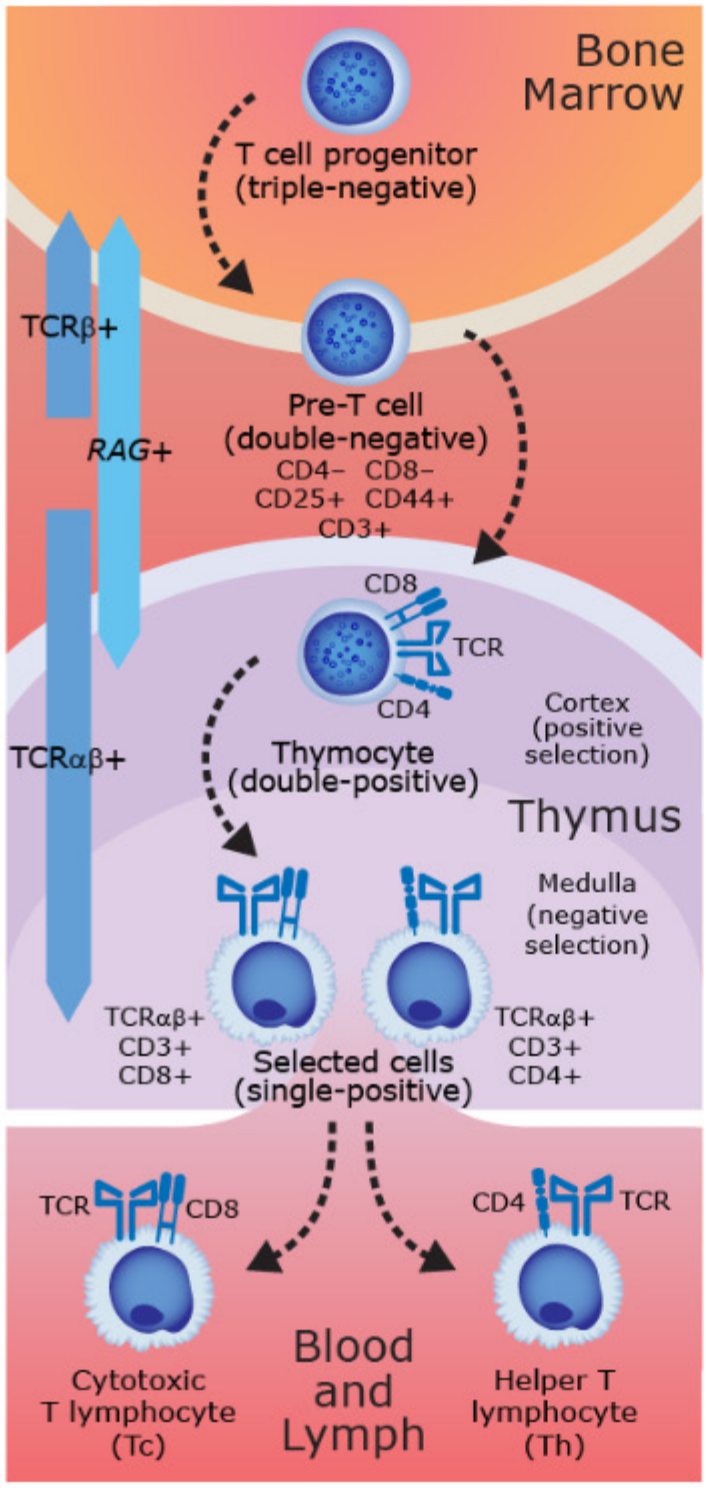

▲ **Figure 2–4.2D** The Ontogeny of T Cells

Connection to Anatomy

The "immunoprivileged" sites of the body are the brain, retina, thymus, testis, and placenta. In each of these cases, a specialized barrier between the organ and the blood prevents exchange of antigens in either direction, and once a pathogen has penetrated such a barrier, immunologic responses to destroy it become more difficult.

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Review Questions Chapters 1–2

1. During a clinical trial, a researcher investigates the effect of intravenous administration of a synthetic glycoprotein, similar in function to IL-5. If this therapy is to be effective in the treatment of patients with selective IgA deficiency, which of the following characteristics of IL-5 must be taken into account to assure similar biologic function?

A. Activation of a specific cell surface receptor
B. Display of cross-species functionality
C. Downregulation of cell growth
D. Production by Th2 cells
E. Stimulation of eosinophilia

2. A 3-year-old boy is discovered to have a genetic mutation that results in deficient production of IL-11. A bone marrow smear would most likely show a deficiency in which of the following cell types?

A. T lymphocytes
B. B lymphocytes
C. Erythrocytes
D. Megakaryocytes
E. Polymorphonuclear cells

3. A patient has a complete blood count performed, and a peripheral blood smear is examined. The blood smear contains a cell that is approximately 10 microns in diameter with a dense basophilic nucleus that almost fills the cell. Which of the following is an important function of this cell?

A. Abscess formation
B. Antibody secretion
C. Destruction of virus-infected cells
D. Phagocytosis
E. Release of vasoactive amines

4. During his annual physical examination, a 50-year-old African-American man complains to his physician of fatigue, swollen cervical lymph nodes, and pain in his spine and ribs. Serum electrophoresis shows a spike of protein in the gamma region. The abnormal immunoglobulin is determined to be of the IgG isotype. An IgG molecule is composed of which of the following?

A. One alpha, one gamma, and two kappa chains
B. One gamma chain and two kappa chains
C. Two gamma chains, one kappa, and one lambda chain
D. Two gamma chains and two kappa chains
E. Two mu chains and two kappa chains

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Chapters 1–2 Review Questions

5. A precursor thymocyte possesses 100 V segment genes, 50 J segment genes, 10 D segment genes, and two constant region genes to rearrange during beta chain synthesis. Assuming that Tdt is not active, how many distinct idiotypes could be created by combining this beta chain with one alpha chain?

A. 162
B. 320
C. 5000
D. 50,000
E. 100,000

6. Cells passing through the thymic cortex are exposed to normal self antigens during their development. Which of the following is true of the most important molecule in the production of single-positive CD4+ helper cells?

A. It is composed of two chains of similar length
B. It is expressed on all nucleated cells
C. Its configuration is maintained by beta-2 microglobulin
D. Its gene products are A, B, and C
E. It presents peptides created inside the cell

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Review Answers Chapters 1–2

1. The correct answer is E. Interleukin-5 acts in the bone marrow to stimulate eosinophil production. In the submucosa it stimulates IgA isotype switching.

2. The correct answer is D. Interleukin-11 has basically the same function as thrombopoietin. It stimulates production of megakaryocytes and platelets.

3. The correct answer is C. The cell described is a lymphocyte, and the various subcategories (B, T, or NK cell) cannot be distinguished on a simple blood film. Therefore, although multiple roles for lymphocytes could have been described, the only statement on this list that is true is that cytotoxic T lymphocytes kill virus-infected cells.

4. The correct answer is D. This patient has multiple myeloma and the malignant plasma cell is producing IgG. All antibodies are made of two heavy and two light chains. Immunoglobulin G is specifically made of two gamma heavy chains and then two identical light chains, so the two kappa or two lambda statements both would have been correct answers.

5. The correct answer is D. The idiotype of the T cell receptor is created by VDJ rearrangement in the bone marrow and thymus. To determine how many possible distinct variable domains could be created, multiply the number of possibilities, but do NOT use the number given for constant domains. The constant domains dictate the isotype of the molecule, not the idiotype.

6. The correct answer is A. CD4+ cells recognize MHC class 2 molecules that are composed of alpha and beta chains of similar length, are expressed only on antigen-presenting cells, and present peptides that have been ingested or endocytosed by the cell. The gene products of MHC class 2 are called DP, DQ, and DR.

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CHAPTER 3 Immunologic Surveillance: Lymphocyte Recirculation

1 Overview of Lymphocyte Recirculation

The fully committed lymphocytes that leave the bone marrow and thymus are said to be "naive." That is, they have never met the antigen that is complementary to their unique antigen receptor. Nor have they yet specialized to become the *effector cells* that destroy and remove the invading pathogen.

Because of the presence of unique *adhesion molecules* on different classes of lymphocytes, naive immune cells *recirculate* and "home" to particular areas of the *secondary lymphoid organs* (spleen, lymph nodes, and mucosal-associated lymphoid tissues). It is estimated that every lymphocyte checks into every lymph node in the body on average once a day, and passes through the spleen on average every other day. This surprising rate of lymphocyte traffic makes surveillance of the entire multicellular organism possible.

If a mature, naive lymphocyte meets its cognate antigen as it passes through one of these organs, it stops there and becomes activated. Activation causes the production of clones of identical lymphocytes—this is why lymphadenopathy is a normal sequela of any immune response. If not so stimulated, these lymphocytes circulate only a few days and then must be replaced from the bone marrow pool.

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the structure and function of the spleen, lymph nodes, and mucosal-associated lymphoid tissues.
- Identify the cellular compartmentalization of immunologic organs for T cells, B cells, and antigen-presenting cells.
- Describe the role of adhesion molecules in lymphocyte trafficking.

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2 Secondary Lymphoid Organs

The secondary lymphoid organs are specially evolved to be sites within the body where naive immune cells have the maximum possibility of meeting and responding to antigen.

2.1 Lymph Nodes

The lymph nodes of the body are kidney-bean-shaped structures designed to filter antigens incoming from the tissue spaces.

2.1.1 Architecture

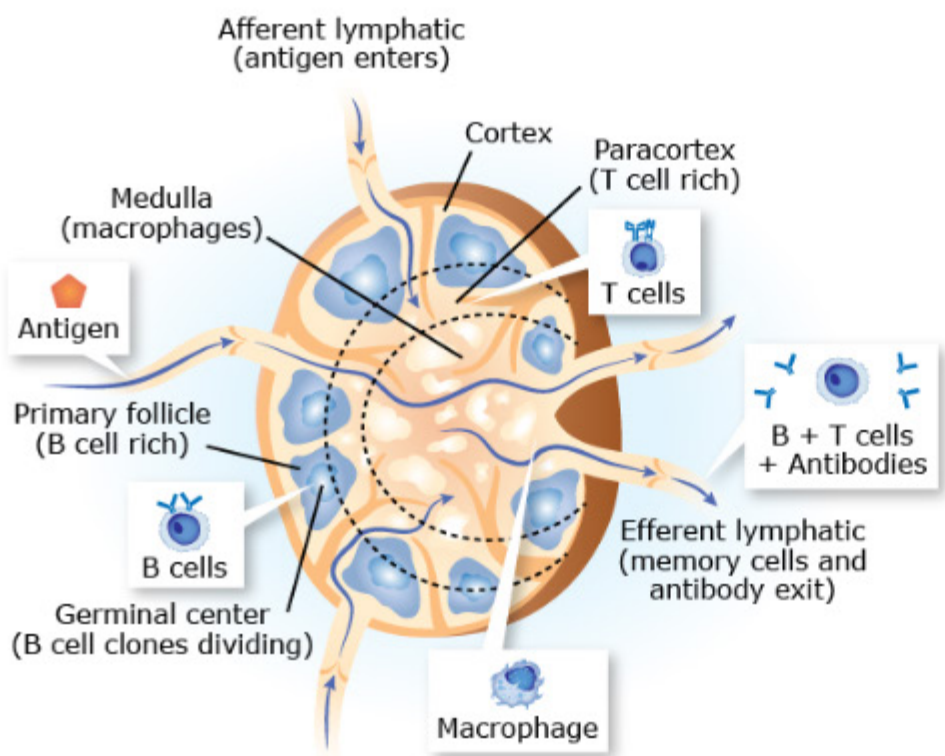
Lymph enters each lymph node through *afferent lymphatics* that punctuate the organ's fibrous capsule. The fluid then percolates through a subcapsular sinus into the outer cortex, then to the inner medulla, and finally into the medullary sinus, which exits the lymph node through a hilum. Fluid from *efferent lymphatic* vessels is ultimately collected into the thoracic duct, which empties into the vena cava.

2.1.2 Cellular Homing

Lymphocytes from the bone marrow and thymus enter the lymph nodes through *high endothelial venules (HEVs)*. The different patterns of expression of cell surface adhesion molecules on T cells and B cells promote accumulation of cells in specific lymph node regions:

- T lymphocytes migrate to the *paracortical areas*.
- B cells produce *primary follicles* in the cortex of the lymph nodes—if specific antigenic stimulation occurs, clones of antigen-specific B cells produce *germinal centers*.

The attraction of different categories of lymphocytes to different areas of the lymph nodes is mediated by chemokine gradients and the binding between *L-selectins* on the lymphocytes and *addressins* on the HEVs. Macrophages tend to accumulate in the *medullary cords*.



▲ **Figure 3-2.1** Anatomy of the Lymph Node

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2.2 Spleen

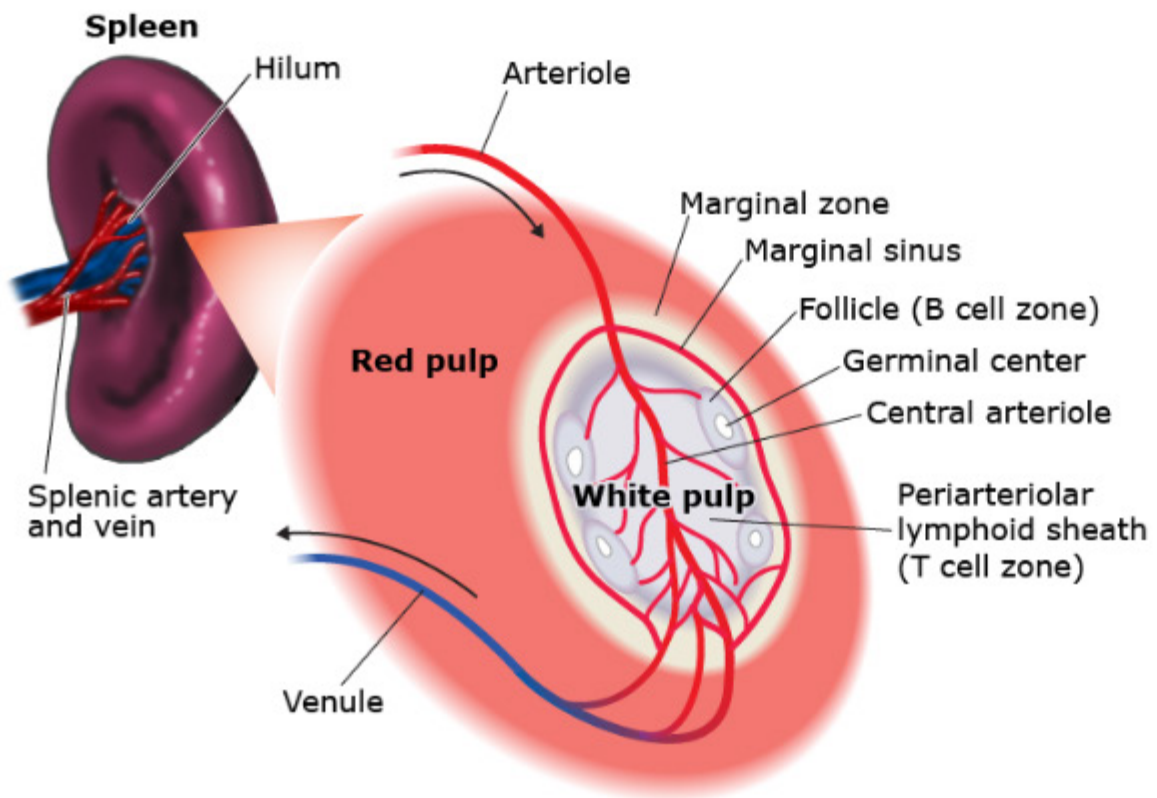
The spleen is the largest lymphoid organ in the adult. It plays the dual role of removing aged or injured red blood cells in the *red pulp* and producing antibodies in the *white pulp*.

2.2.1 Architecture

The spleen is supplied by the single splenic artery entering the capsule at the hilum. The arterioles branching from this become surrounded with lymphoid sheaths, which make up the white pulp. The arterioles terminate in sinusoids, which comprise the red pulp. Any antigen entering the blood is filtered out and responded to within the spleen.

2.2.2 Cellular Homing

Naive T cells home to the *periarteriolar lymphoid sheaths (PALS)* of the white pulp and naive B cells create a *corona* of follicles outside of the T cell area.



▲ **Figure 3-2.2** Anatomy of the Spleen

2.3 Mucosal-Associated Lymphoid Tissues (MALT)

The mucosal-associated lymphoid tissues tend to be less organized accumulations of lymphocytes that provide protection against antigens entering the body across the mucosal surfaces. During the memory response, B and T memory cells, dedicated to collaborating to produce IgA antibodies, home to mucosal surfaces to respond if any pathogen tries to repenetrate these barriers.

Connection to

Microbiology and Physiology

Because blood entering the spleen passes into sinusoids that have much greater volume than the blood vessels through which they entered, the flow of blood is slowed. This slower flow allows phagocytes lining the sinusoids to cleanse particulate debris from the blood with greater efficiency. Patients who have had surgical *splenectomies* or those who have autosplenectomized (sickle cell patients) are at much greater risk of dangerous infections involving *encapsulated organisms* that enter the bloodstream. This is because bacterial and fungal capsules make these organisms difficult to phagocytize, and trapping them in the sinusoids of the spleen with antibodies and phagocytes is one of the only efficient protective immune responses.

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1 Overview of Acute Inflammation

Acute inflammation is the body's response to virtually any injury or invasion. Although some of acute inflammation's cardinal signs are unpleasant (redness, swelling, heat, pain, loss of function), it plays the critical role of calling in the innate immune system's first responders (phagocytes), beginning the chemical and physical processes that stop further invasion and activating the acquired immune response.

Circulating leukocytes are attracted to areas of acute inflammation due to the increased blood flow and the vascular dilatation it engenders. Neutrophils are the first responders, peaking within six hours, followed by monocytes and even eosinophils five to six hours later in response to neutrophil-produced mediators. These cells extravasate into the area of injury or invasion following chemical gradients of cytokines and inflammatory mediators. Selectin-type adhesion molecules expressed on the inflamed endothelium promote the attachment and diapedesis of leukocyes into the area.

2 Chemotaxis

A variety of small chemicals produced in the area of injury serve as *chemoattractants* for phagocytic cells to enter the area.

▼Table 4-2.0 Chemotaxins

Chemotaxin	Source
Leukotriene B4	Phospholipid membrane damage activates the arachidonic acid cascade and lipoxygenase pathway
Interleukin-8	Resident and entering leukocytes
C5a	Classical, alternative, or lectin complement cascades
Formyl methionyl peptides	Bacteria introduced into the injury site
Fibrinopeptides	Activation of the clotting cascade

USMLE® Key Concepts

For Step 1, you must be able to:

- List the sequence of steps involved in acute inflammation.
- Describe the types and sources of molecules involved in chemotaxis.
- Explain the mechanisms of phagocytosis and intracellular killing.
- Identify the molecular basis and role of opsonization.
- Describe the molecular basis of pathogenesis for leukocyte adhesion deficiency (LAD) and chronic granulomatous disease (CGD).

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3 Diapedesis

The process by which leukocytes leave the vasculature to enter an area of acute inflammation, *diapedesis*, involves four steps: rolling, activation, tight adhesion, and extravasation/transmigration.

3.1 Rolling

The first leukocyte responders travel to the area of inflammation at the same speed as the blood moving through the body. However, as they near the area of inflammation, they are slowed by the dilation of vascular channels. Low-affinity binding between leukocyte membranes *(addressins)* and the surface of the injured endothelium *(E-selectins)* causes the leukocytes to attach and detach repeatedly and roll along the endothelial surface.

3.2 Activation

Resident cells (mast cells and macrophages), invading microbes, and newly arriving inflammatory cells stimulate the release of chemoattractants within the area of inflammation. These small chemicals bind to the phagocyte membrane and trigger a conformational change in the affinity of *integrin* molecules on their surfaces.

3.3 Tight Adhesion

The activated integrin molecules on phagocytes become complementary to adhesion molecules on the endothelium, which are called *immunoglobulin superfamily cellular adhesion molecules (ICAMs)*. This final binding step causes the leukocytes to arrest their progress and bind tightly to the endothelial surface.

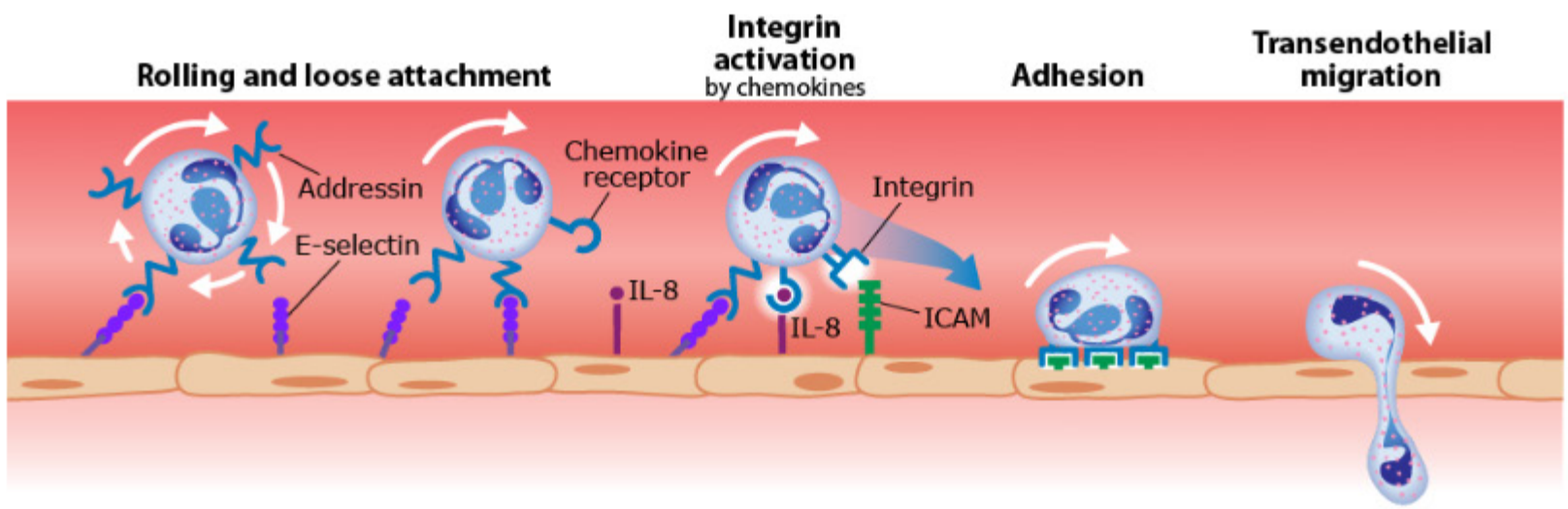
3.4 Extravasation and Transmigration

The adherent phagocyte now simply extends its pseudopodia through the endothelium and extravasates into the area of injury following the chemical gradient.

Memory Aid

The interaction between *selectins* and *addressins* always mediates *loose binding* between cells. The interaction between *integrin* and *ICAM* always mediates *tight binding*.

To remember the distinction between the function of these adhesion molecules in normal lymphocyte recirculation versus acute inflammation, simply think who is controlling the process: in *lymphocyte recirculation*, the Lymphocyte is *selecting* and the *endothelium* is being *addressed*. In *acute inflammation*, the endothelium is sending a signal to passersby in the circulation, so it is the *E-selecting*, and the *leukocyte* is being *addressed*.



▲ **Figure 4-3.4A** Steps of Leukocyte Extravasation

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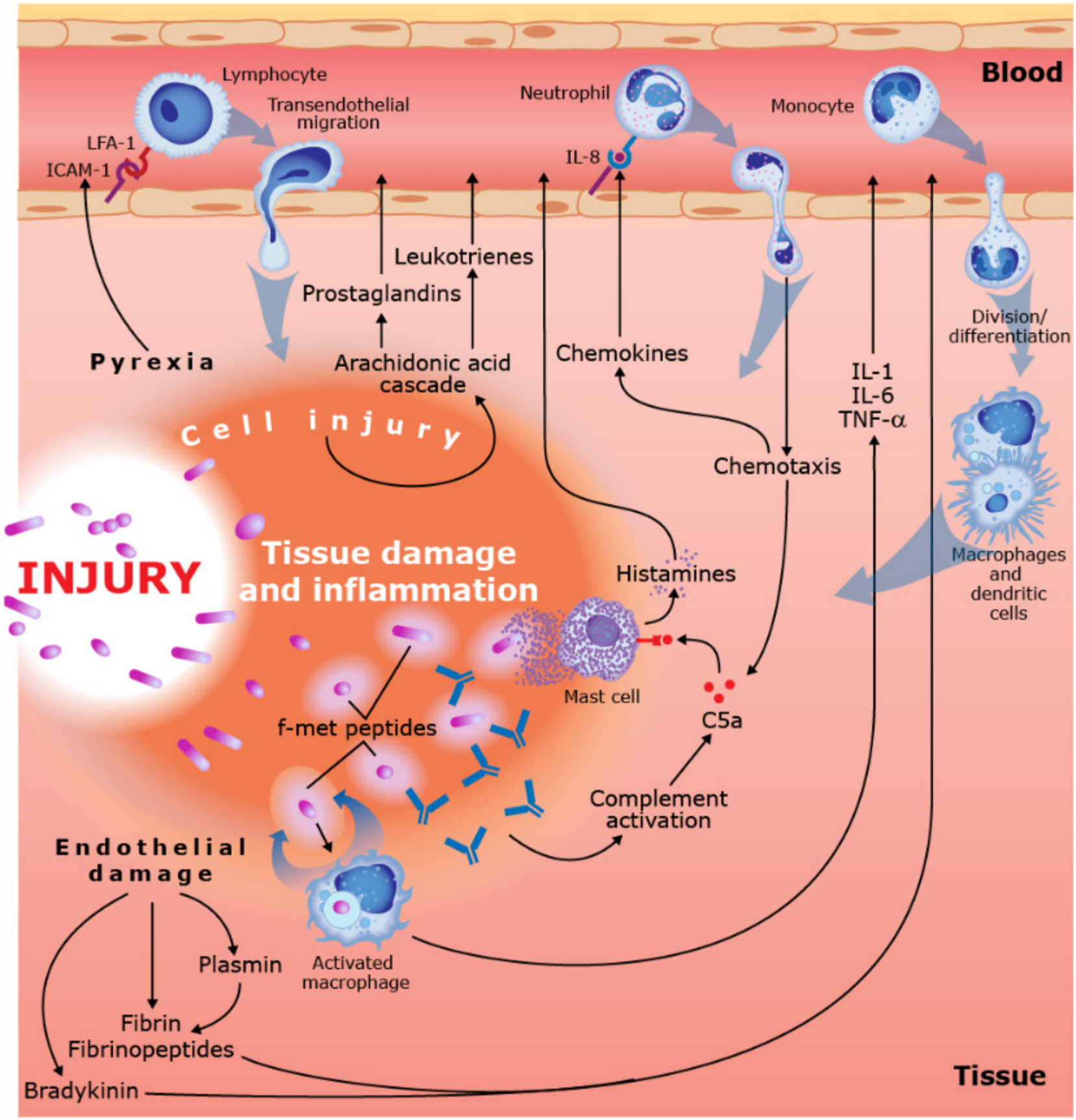

▲ **Figure 4-3.4B** Acute Inflammatory Response

Clinical Application

Leukocyte adhesion deficiency type I (LAD 1) results from failure to produce CD18, which is the common β2 subunit of the β2 integrins (LFA-1 family). β2 integrins are involved in leukocyte diapedesis, but also serve as receptors for C3b to promote opsonization and phagocytosis. Binding of β2 integrins to their ICAM ligands induces intracellular signaling that is important for a host of other cellular functions including cytokine production, cytotoxicity, apoptosis, and proliferation. Microbial infections can be handled temporarily with antibiotics in these patients, but the long-term solution is bone marrow transplantation.

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4 Recognizing Nonself

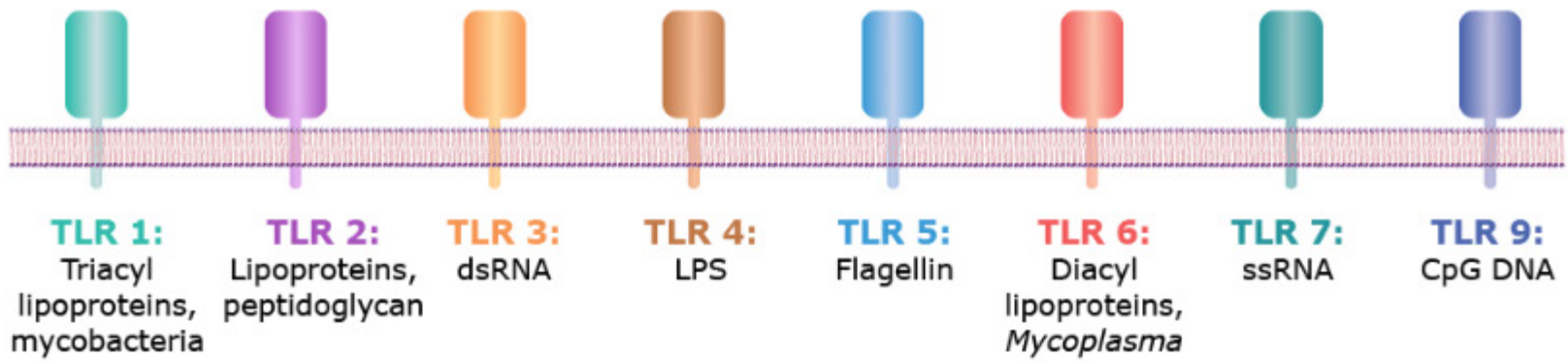
The ability of phagocytes to discriminate between friend and foe is essential to the working of a healthy immune response.

4.1 Pathogen-Associated Molecular Patterns (PAMPs)

Discrimination between self and non-self is accomplished through the recognition of *pathogen-associated molecular patterns (PAMPs)* by pattern recognition receptors (PRRs).

4.2 Toll-Like Receptors (TLRs)

One category of pattern recognition receptors, the *toll-like receptors (TLRs)*, binds with considerable specificity to the rigid surface sugars found on microbial surfaces. Binding can be activated by bacterial peptidoglycan, flagellin and lipoproteins, mycobacterial lipoarabinomannan, and yeast zymosan. Other TLRs found on endosomal membranes are engaged by viral double-stranded RNA or unmethylated bacterial DNA. Regardless, once these receptors are engaged, nuclear factor κB (NFκB) and other transcription factors direct the expression of a variety of antimicrobial products.



▲ **Figure 4-4.2** Toll-Like Receptors

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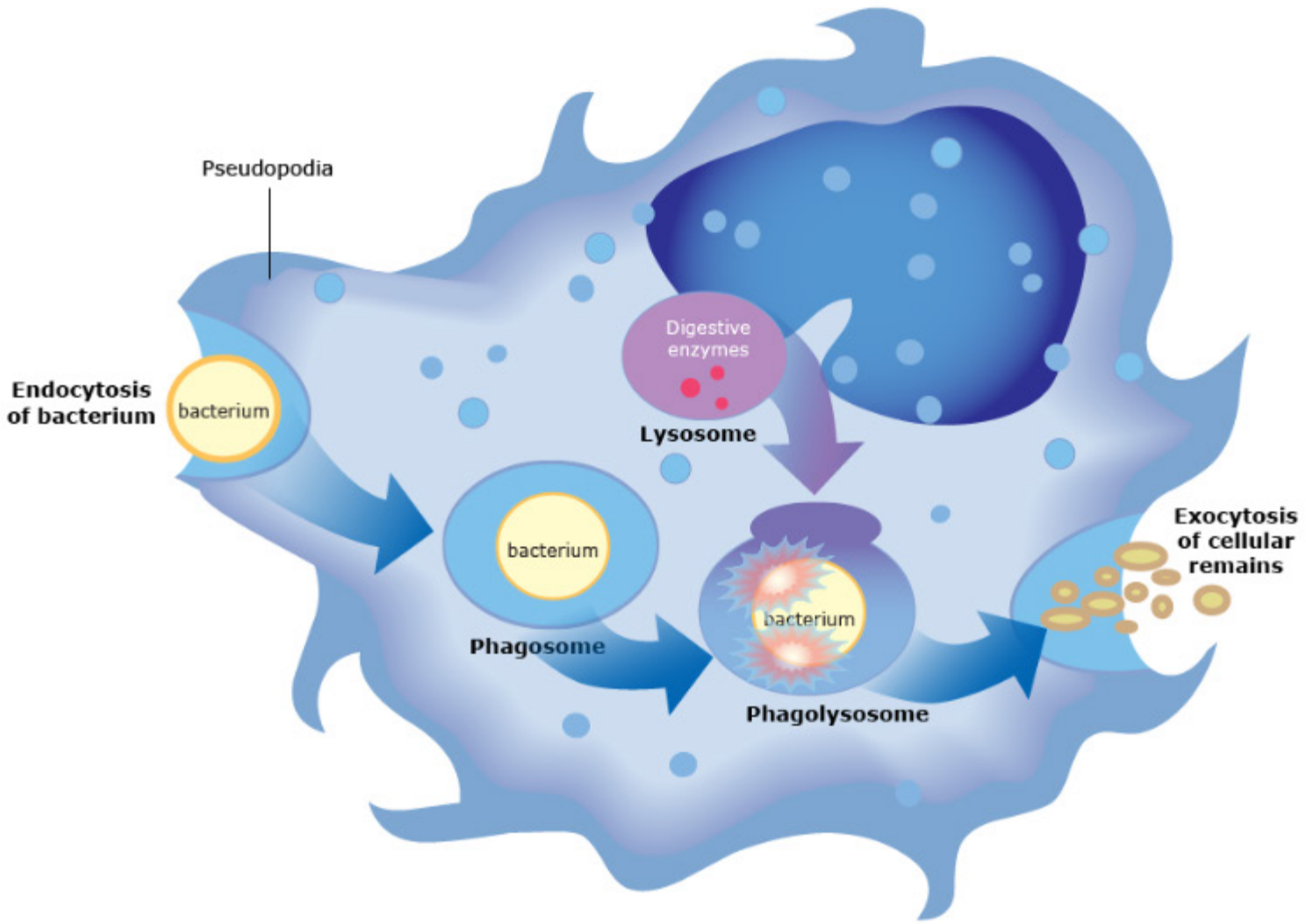
5 Phagocytosis

A common trait shared by the immune cells that first enter the area of inflammation is that they are phagocytic: They ingest and digest particulate debris from the injury and any invading microbes.

5.1 Steps of Phagocytosis

Phagocytosis is a process that includes the following:

- Use of pseudopodia by the phagocyte to engulf the non-self particle.
- Fusion of the pseudopodia with the non-self particle to create a phagosome.
- Addition of digestive enzymes within lysosomes to create the phagolysosome.
- Intracellular digestion of the non-self particle.
- Exocytosis of digested debris.



▲ **Figure 4-5.1** Phagocytosis

5.2 Opsonization

Opsonization is possible in the area of inflammation if either immunoglobulin G (IgG) or complement component 3b (C3b) are available. This process involves the coating of non-self particles with IgG, C3b, or both in such a way that the non-bound end can then fit into a complementary receptor on the surface of a phagocyte. This process has been shown to enhance the speed of phagocytic engulfment by up to 4,000-fold.

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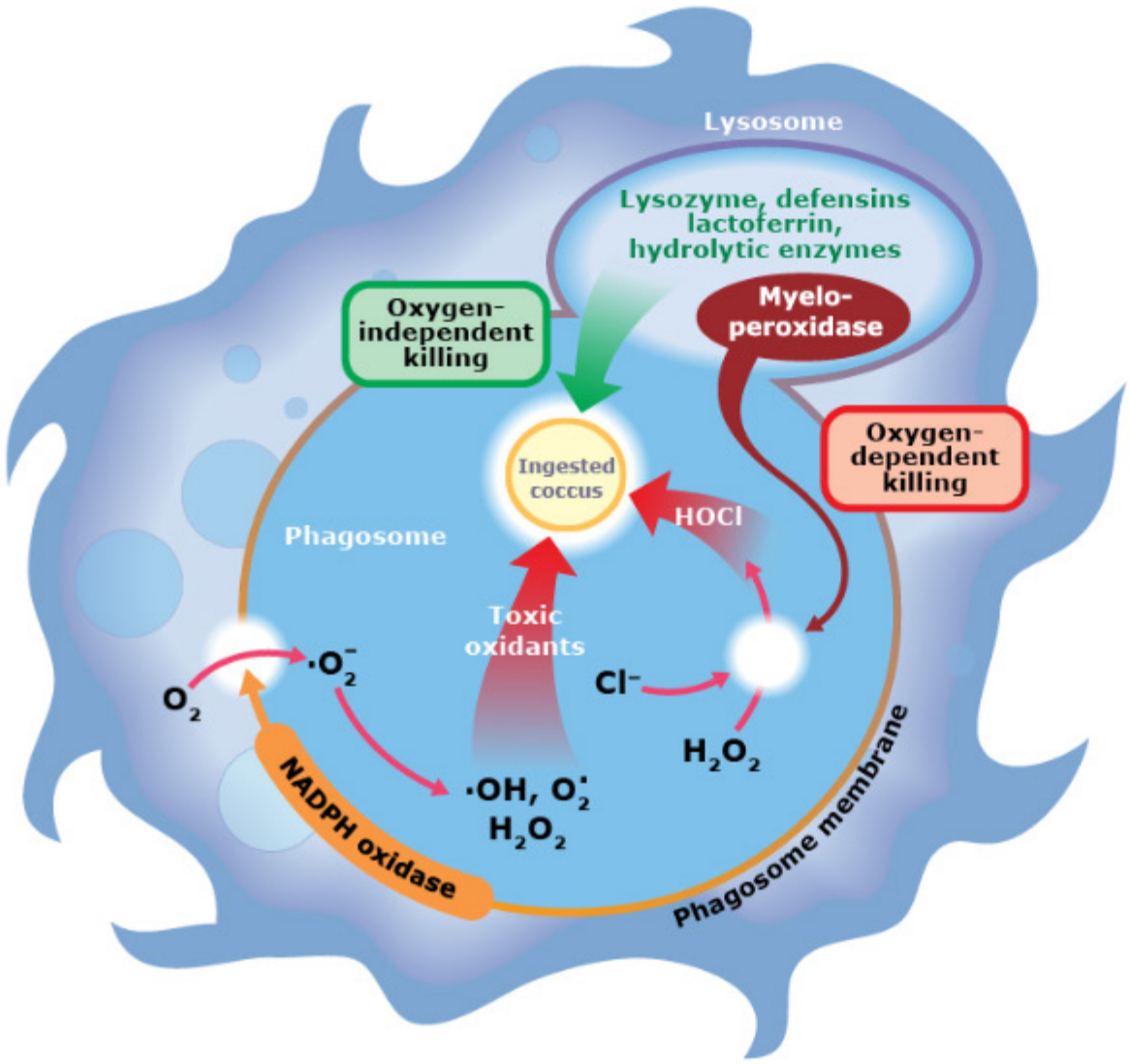
5.3 Mechanisms of Intracellular Killing

Once engulfment has taken place, a respiratory burst in phagocytes causes activation of a membrane bound oxidase, *NADPH oxidase*. This enzyme reduces oxygen to superoxide anion which then generates hydroxyl radical and hydrogen peroxide. These oxygen radicals formed inside the phagolysosome are all microbicidal. *Myeloperoxidase* is added with the lysosomes and acts on hydrogen peroxide with chloride ions to produce hypochlorite (bleach). The remainder of the lysosomal contents include oxygen-independent digestive enzymes such as lysozyme, defensins, and lactoferrin.



▲ **Figure 4-5.3A** Mechanisms of Intracellular Killing

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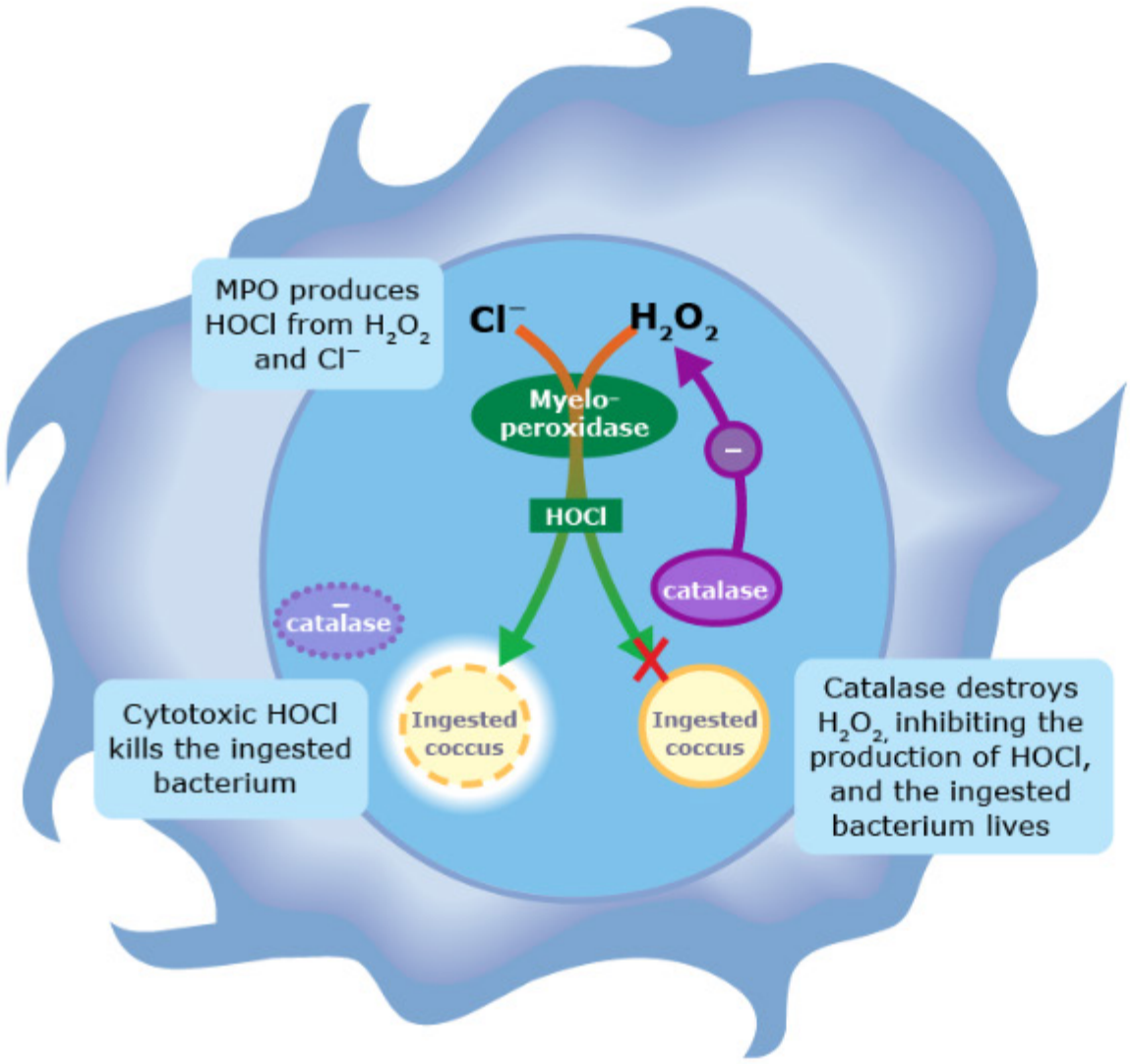

▲ **Figure 4-5.3B** Intracellular Killing in CGD

Memory Aid

Staph '**N** **E**nterobacteriaceae **A**re **L**isted **C**atalase **P**ositive:

***S**taphylococcus*

***N**ocardia*

***E**nterobacteriaceae*

***A**spergillus*

***L**isteria*

***C**andida*

***P**seudomonas*

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Processing and Presentation of Antigens

1 Overview of Antigen-Presenting Cells

Following the influx and activation of phagocytic cells in areas of injury and inflammation, the cells' phagocytosis of non-self particles and cellular debris prepares them to become *antigen-presenting cells*. Often, the most efficient of these cells are the resident dendritic cells of the epithelia, which transport their ingested antigens to the first available secondary lymphoid organ, where the activation of the lymphocytes begins.

2 Pathways for Loading MHC Molecules With Peptides

Since T lymphocytes can only "see" peptides that are presented to them by antigen-presenting cells, the processing of these fragments has a key role in determination of the ultimate immune response.

2.1 MHC Class 1

In all normal, nucleated cells, MHC class 1 molecules are synthesized in the endoplasmic reticulum. Other proteins produced in the cytosol are degraded in proteasomes and transported via the *TAP complex* to the endoplasmic reticulum, where they become bound in the grooves of newly formed class 1 molecules. This complex of MHC 1 and peptide is now transported to the cell surface, where it is expressed on the membrane. This is referred to as the *endogenous pathway* of MHC loading.

If a cell is making normal proteins, and the thymus did its job to produce *central tolerance* to self proteins, there should be no cells in the body that would recognize such peptides loaded into MHC class 1 molecules.

In the case of an infection with intracellular microbes or a pathological alteration of cell function such as malignant transformation, abnormal proteins are loaded into these MHC class 1 molecules, and their presentation on the cell membrane serves as the signal to the acquired immune response to kill the damaged cell. In such cases, *CD8+ cytotoxic T cells (Tc)* recognize the combination of *MHC class 1 and altered self peptide* and destroy the target cell.

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the mechanisms of peptide loading and the functions of MHC class 1 and 2 presentation.
- Describe the functional roles and means of macrophage subpopulation activation.
- List the steps of Th cell activation.
- Explain the pathogenesis of superantigens.
- Identify the means of activation and the functions of Th cell subpopulations.

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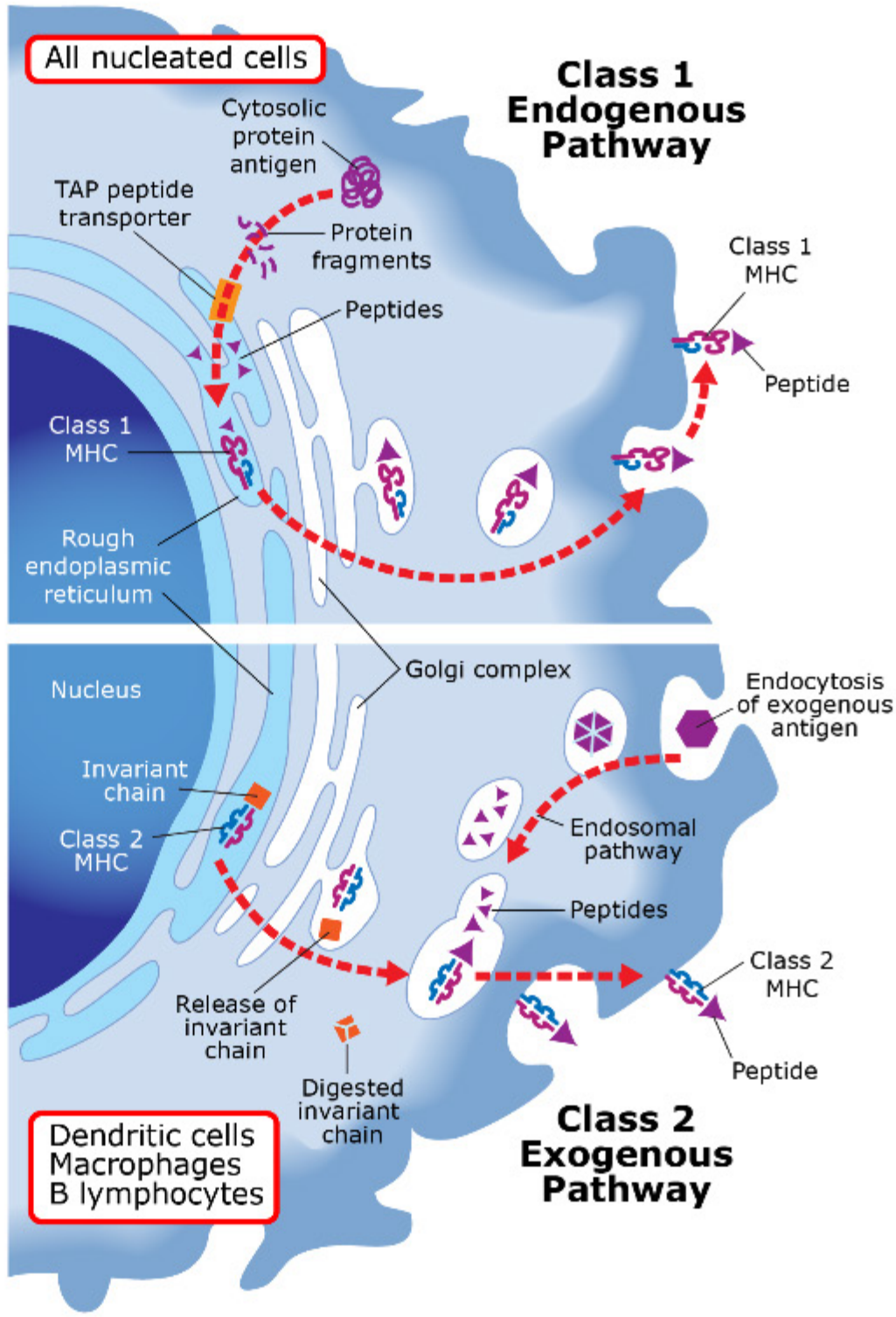
2.2 MHC Class 2

MHC class 2 molecules are similarly synthesized in the endoplasmic reticulum, but only in *antigen-presenting cells (APCs)*, which include macrophages, dendritic cells, B lymphocytes, activated T cells, and activated endothelial cells. What these seemingly diverse populations of cells have in common is their ability to phagocytose or endocytose and partially digest proteins in acidic vesicles. This is necessary for MHC class 2 peptide loading because the class 2 molecule is created with an invariant chain blocking the peptide binding groove.

When the 3-chain precursor molecule is transported to the site of the acidic vesicle, the invariant chain is dissolved away and the site becomes occupied with peptides from the external source. For this reason, the pathway of MHC class 2 loading is referred to as being *exogenous* or *endosomal*. The lymphocyte that becomes attracted to and activated by the *MHC class 2 and peptide complex* is the *CD4+ T helper (Th)* cell.



▲ **Figure 5-2.2** Major Histocompatibility Complex

▼ **Table 5-2.2** MHC Class 1 and MHC Class 2

	MHC Class 1	MHC Class 2
Gene products	HLA-A, -B, -C	HLA-DP, DQ, DR
Cell distribution	All nucleated cells, platelets	B lymphocytes, macrophages, dendritic cells, activated T cells, activated endothelial cells
Invariant chain	No	Yes
β2 Microglobulin	Yes	No
Peptide source	Endogenously synthesized	Exogenously processed
Recognition by	Tc (CD8+ T lymphocytes)	Th (CD4+ T lymphocytes)
Function	Killing of abnormal cells	Elicitation of T cell help

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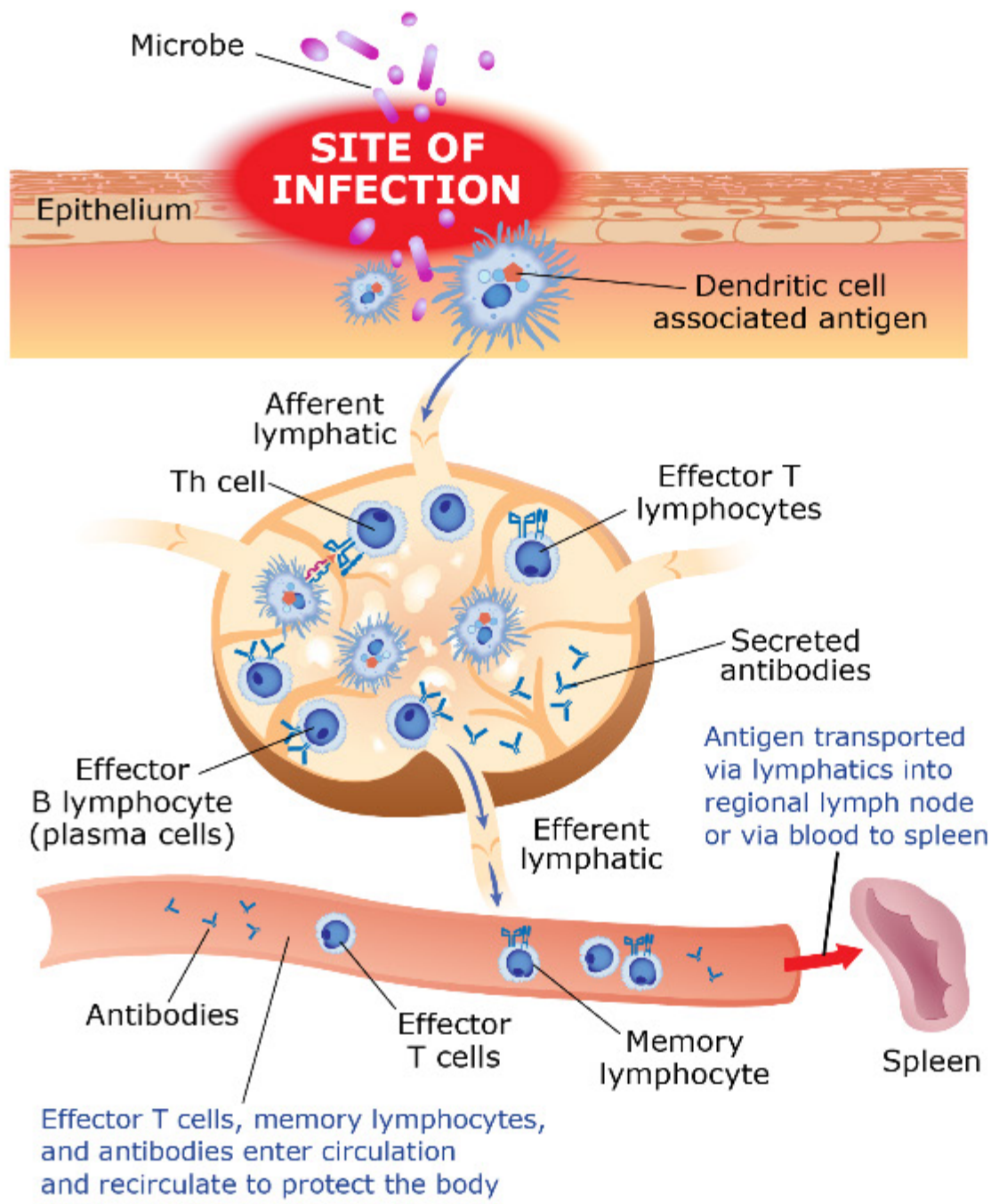
3 Transportation of Antigen to Secondary Lymphoid Organs

As APCs ingest and digest the foreign particles and debris from the initial inflammatory lesion, within hours they begin to transport that material to the closest draining secondary lymphoid organ. Dendritic cells are the most efficient at the process of antigen trapping and transport, and as they arrive in the lymph nodes (entering through lymphatics from the tissue fluids) or the spleen (if carried via the blood), their surfaces are covered with MHC class 2 and peptide complexes. As they become trapped in the meshwork of these organs, mature, naive lymphocytes in their cycle of recirculation have their first opportunity to bind with their cognate antigens on the APC membrane.



▲ **Figure 5-3.0** Antigen Transport to Secondary Lymphoid Organs

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4 Differentiation of Macrophage Populations

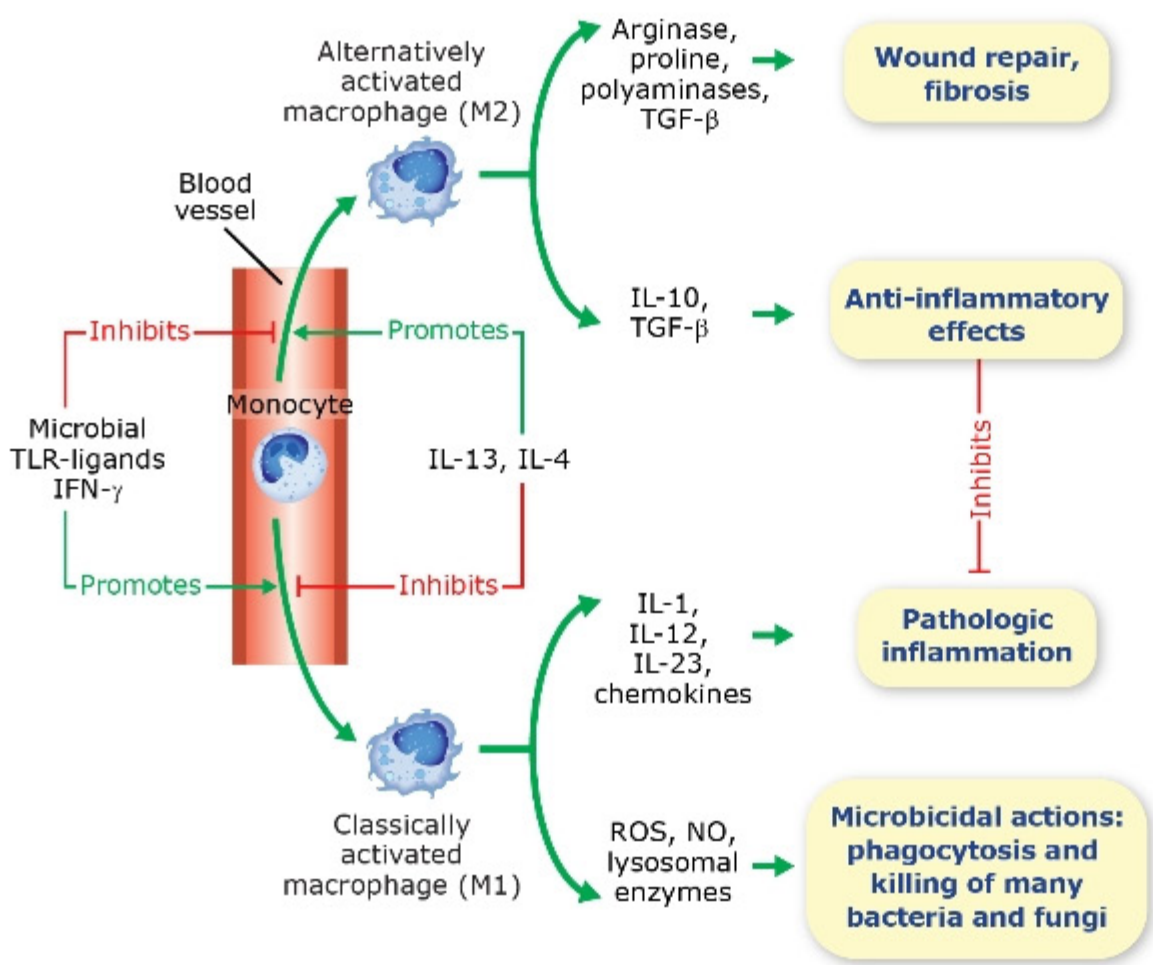
Depending on the environment in which monocytes are exposed to foreign particles, they differentiate down one of two pathways that make them a pivotal force in the evolution of the protective immune response.

4.1 Classically Activated Macrophages (M1)

Monocytes entering an area of inflammation from the vasculature undergo a terminal differentiation into *M1 macrophages* if they are exposed to *interferon-γ* or *microbial TLR ligands*. M1 cells become key in killing many facultative intracellular pathogens that live inside the phagocytic cells of the human body. Carried to the chronic inflammatory level, M1 cells are strongly involved in pathologic inflammation.

4.2 Alternatively Activated Macrophages (M2)

Monocytes exposed to *interleukin (IL)-13* or *IL-4* undergo a terminal differentiation into M2 cells, which become crucial in wound repair and fibrosis. M2 cells express an anti-inflammatory effect during chronic inflammation.



▲ **Figure 5-4.0** Macrophage Subpopulations

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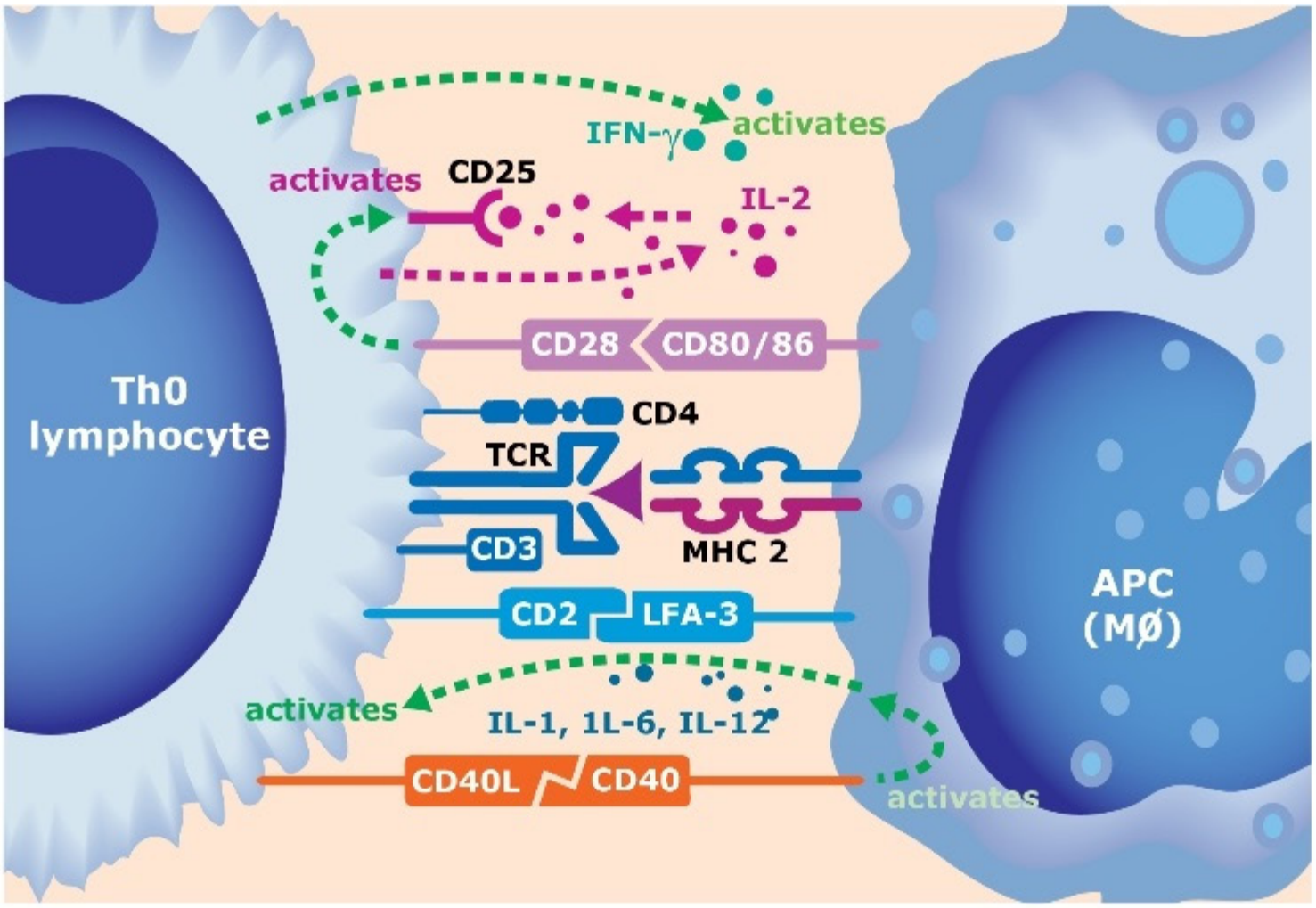
5 Activation of T Helper Cells

The presentation of MHC 2-peptide complexes on APCs to antigen-specific, naive CD4+ T lymphocytes begins the process of Th cell activation in the secondary lymphoid organs. This process occurs in three steps, with only the interaction between the TCR and the MHC complex being antigen-specific.

1. Specific TCR binds to MHC/peptide complex.
2. Costimulatory molecules are engaged.
   - Integrins bind to ICAMs.
   - CD4 stabilizes binding between MHC class 2 and TCR.
   - CD28 binds to B7 (CD80).
3. Cytokine synthesis activates cells.
   - Macrophage produces IL-1, IL-6, and tumor necrosis factor-α (TNF-α).
   - Th cell produces interferon-γ (IFN-γ) and IL-2.

These steps cause the production of activated, "angry" M1 macrophages, and the binding of IL-2 to the Th cell's own high-affinity IL-2 receptor (CD25) causes that cell to clone itself into many identical, antigen-specific Th cells. If, by contrast, there is binding of macrophage surface B7 by cytotoxic T lymphocyte-associated protein 4 (CTLA-4), an inhibitory signal is given and the activity of the Th cell is down-regulated.

Mechanisms for up-regulation of CTLA-4 expression are under intense study as possible components of the therapy of chronic inflammatory diseases such as Crohn disease and rheumatoid arthritis.



▲ **Figure 5-5.0A** T Cell Activation

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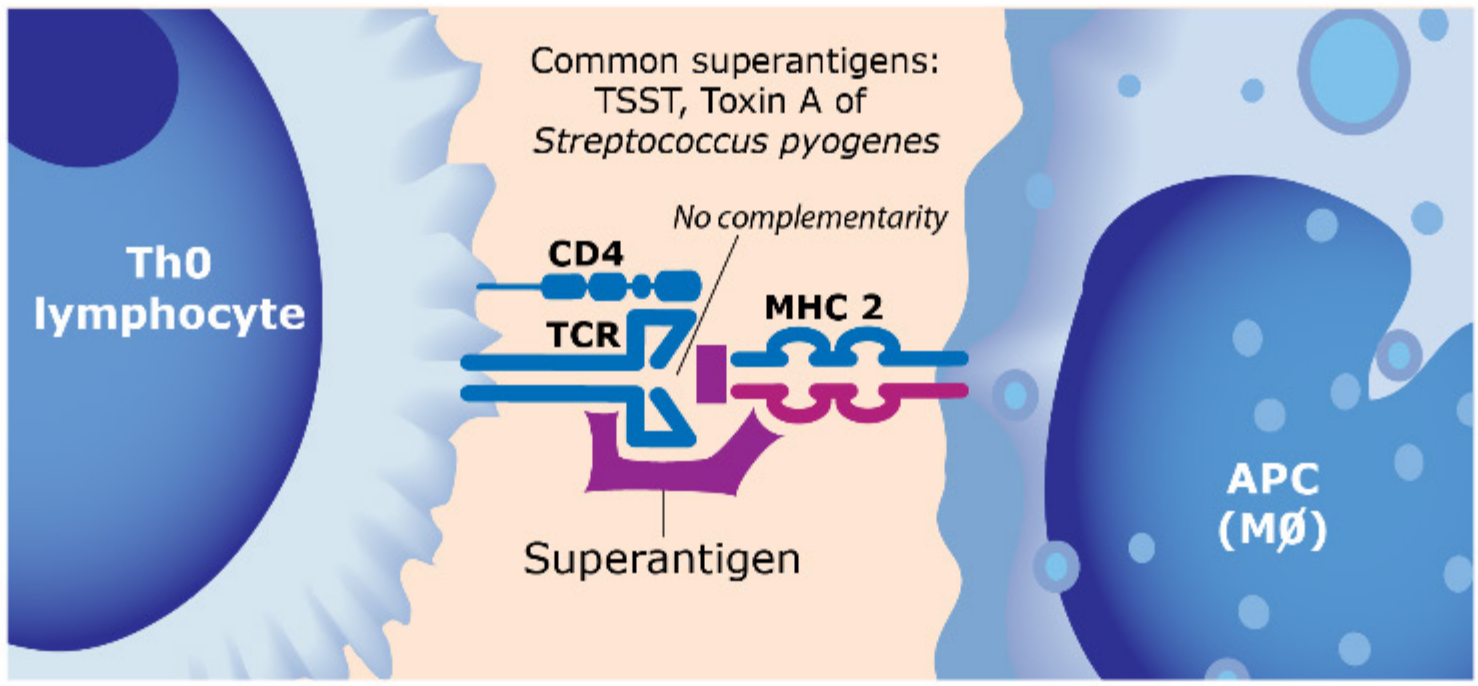
Clinical Application

Superantigens

Soluble products of bacteria or viruses that cause polyclonal stimulation of T cells and macrophages are known as superantigens. They do this by cross-linking the outsides of the TCRs and MHC class 2 molecules on Th cells and macrophages that otherwise have no affinity for each other. Because these cells are being held together in the absence of an antigen-specific signal from the MHC/peptide complex, the remainder of the stimulatory cascade proceeds in a non-specific fashion. Co-stimulatory molecules lock on to one another, signal transduction is activated, and cytokine secretion begins, but in such a volume that the normally helpful cytokines (IL-1, IL-6, TNF-α, IFN-γ, and IL-2) can become life-threatening. Toxic shock syndrome toxin-1 (TSST-1) of *Staphylococcus aureus* and Exotoxins A through C (pyrogenic exotoxins) of *Streptococcus pyogenes* act as superantigens.

Connection to Microbiology

Endotoxin shock, which may occur during infection with gram-negative bacteria, has a mechanism of pathogenesis that is strikingly similar to that of superantigen activation. The initial step of endotoxin shock, however, involves direct binding of *bacterial lipopolysaccharide* from the outer membrane of gram-negatives (endotoxin) to the *CD14 toll-like receptor* possessed by macrophages, monocytes, and dendritic cells. As a result of this direct stimulation, there is over-production of IL-1, IL-6, and TNF-α in a polyclonal fashion, and the patient, as with superantigen activation, dies by virtue of the cytokine storm.



▲ **Figure 5-5.0B** Superantigens

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6 Differentiation of T Helper Cell Subsets

The first T helper cell to be stimulated in response to a new antigenic exposure is the mature, naive Th cell, also referred to as a *Th0*. Depending on the cytokines produced in this initial step of Th activation (M1 or M2 cytokines), the Th0 undergoes further differentiation to become a specialized helper for either *cell-mediated immunity (CMI)* or *antibody-mediated (humoral) immunity (HI)*.

The choice of Th differentiation pathway is dictated by the category of pathogen and the type of macrophage differentiation that has occurred in the inflammatory focus. Microbes that stimulate a strong initial innate response with production of IL-12 from M1 macrophages or IFN-γ by NK cells predispose to the production of Th1 cells. In the absence of such stimuli, the "default" loop of differentiation is encouraged by the constitutive production of IL-4 by Th0 cells and stimulation of M2 cells, with the resultant development of Th2 cells.

Because all Th cells are CD3+ and CD4+, these populations are distinguished from one another by the cytokines they produce:

- **Th0:** These *pluripotent Th* cells are capable of making all Th cytokines (IFN-γ, IL-2, IL-4, IL-5, and IL-6).
- **Th1:** As the *organizer of CMI*, these cells retain the ability to produce IFN-γ, IL-2, and TNF-β.
- **Th2:** As the *organizer of HI*, these cells produce IL-4, IL-5, IL-6, IL-10, IL-13, and TGF-β.

Once the differentiation process has begun, it tends to polarize more over time due to complex feedback and reciprocal inhibitory loops. For example, IFN-γ from Th1 cells both stimulates differentiation of more Th1 from Th0 and inhibits the production of Th2. Analogously, IL-4 from the Th2 stimulates production of more Th2 at the same time IL-4 and IL-10 from the same source inhibit the production of Th1 cells.

Two additional Th cells arise from the Th0:

- **Treg:** These cells *inhibit Th1 function* and are functionally anti-inflammatory. They are identified by the expression of transcription factor FoxP3 and constitutive production of CD25 (the receptor for the alpha chain of IL-2). The expansion of clones of Treg cells is favored by the presence of TGF-β and glucocorticoids, and once active, Tregs produce IL-10, IL-35, and TGF-β.

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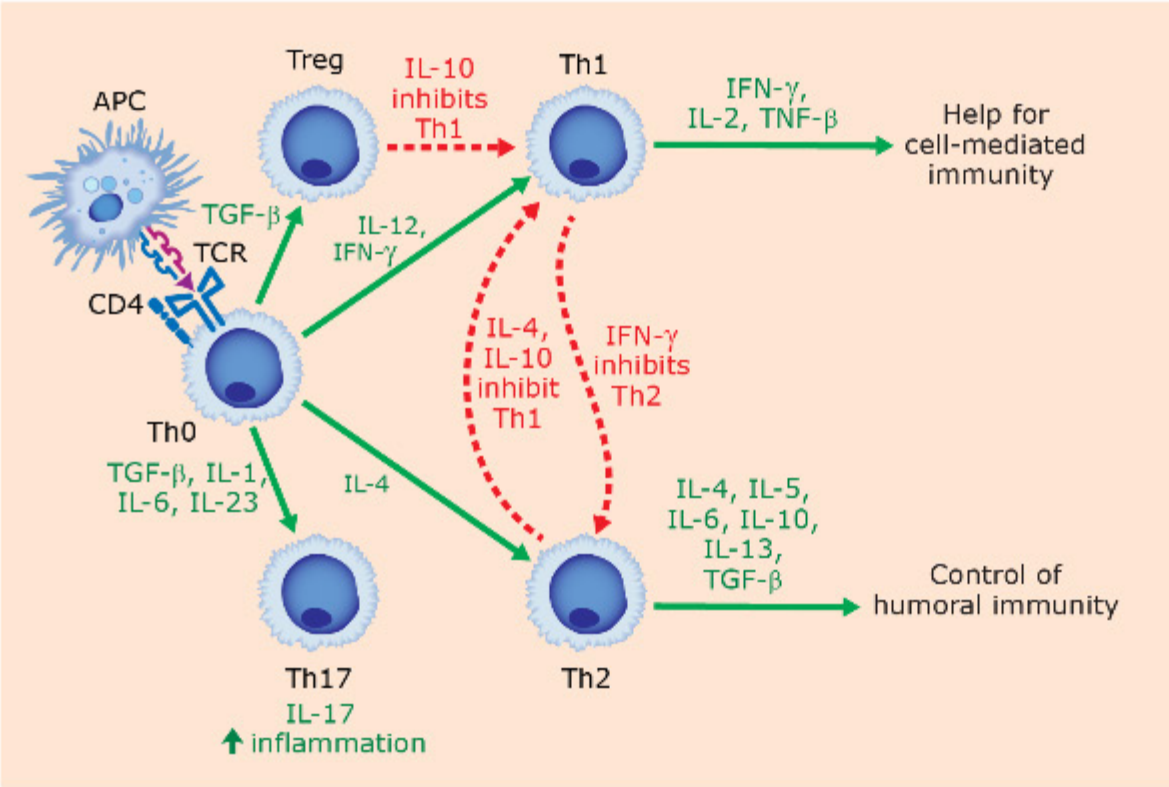
- **Th17:** These *proinflammatory cells* recruit neutrophils and monocytes into their locale. They are identified by their expression of the transcription factor RORgammat as well as their production of IL-17, IL-23, and chemokines. Their activation is induced by the presence of TGF-β, IL-6, IL-1, and IL-23.



▲ **Figure 5-6.0A** T Cell Subpopulations

▼ **Table 5-6.0** Summary of Th Subsets

	Th1	Th2	Treg	Th17
Identification	CD3+, CD4+	CD3+, CD4+	CD3+, CD4+ FoxP3	CD3+, CD4+, RORgammat
Induced by	IFN-γ, IL-12	IL-4	TGF-β, gluco-corticoids	TGF-β, IL-6, IL-1, IL-23
Cytokines produced	IFN-γ, IL-2, Lymphotoxin (LT or TNF-β)	IL-4, IL-5, IL-6, IL-10, IL-13, TGF-β	IL-10, IL-35, TGF-β	IL-17, IL-23, chemokines
Result in	Macrophage activation, stimulation of IgG production	Stimulation of IgE production, activation of mast cells and eosinophils	Inhibition of Th1, anti-inflammatory	Recruitment of neutrophils, monocytes
Defense against	Intracellular microbes	Helminths		Extracellular bacteria, fungi
Role in disease	Chronic autoimmune hyper-sensitivities	Allergies		Chronic autoimmune hyper-sensitivities

Connection to Microbiology

Microbes that live outside of host cells: These are most effectively destroyed by the production of antibodies, activation of complement, and enhancement of phagocytosis: the Th2, *humoral immune response*. This category includes most bacteria, fungi, and parasites.

Microbes that hide inside host cells: These require a different form of immunologic recognition because the host has to recognize the difference between the altered, infected cell and the body's normal cells. In these cases, the cell-mediated, Th1 immune response is most effective, and the choice of the actual effector cell to do the killing is dictated by the category of intracellular pathogen. *Facultative intracellulars*, which survive inside phagocytic cells, are best destroyed by the activation of the phagocyte that is infected to better do its job. Facultative intracellulars include organisms such as *Mycobacterium, Listeria, Histoplasma, Leishmania*, and others. *Obligate intracellulars* such as viruses, rickettsiae, and chlamydiae may be killed by cytotoxic T cells, natural killer cells, or antibody-dependent cell-mediated cytotoxic cells.

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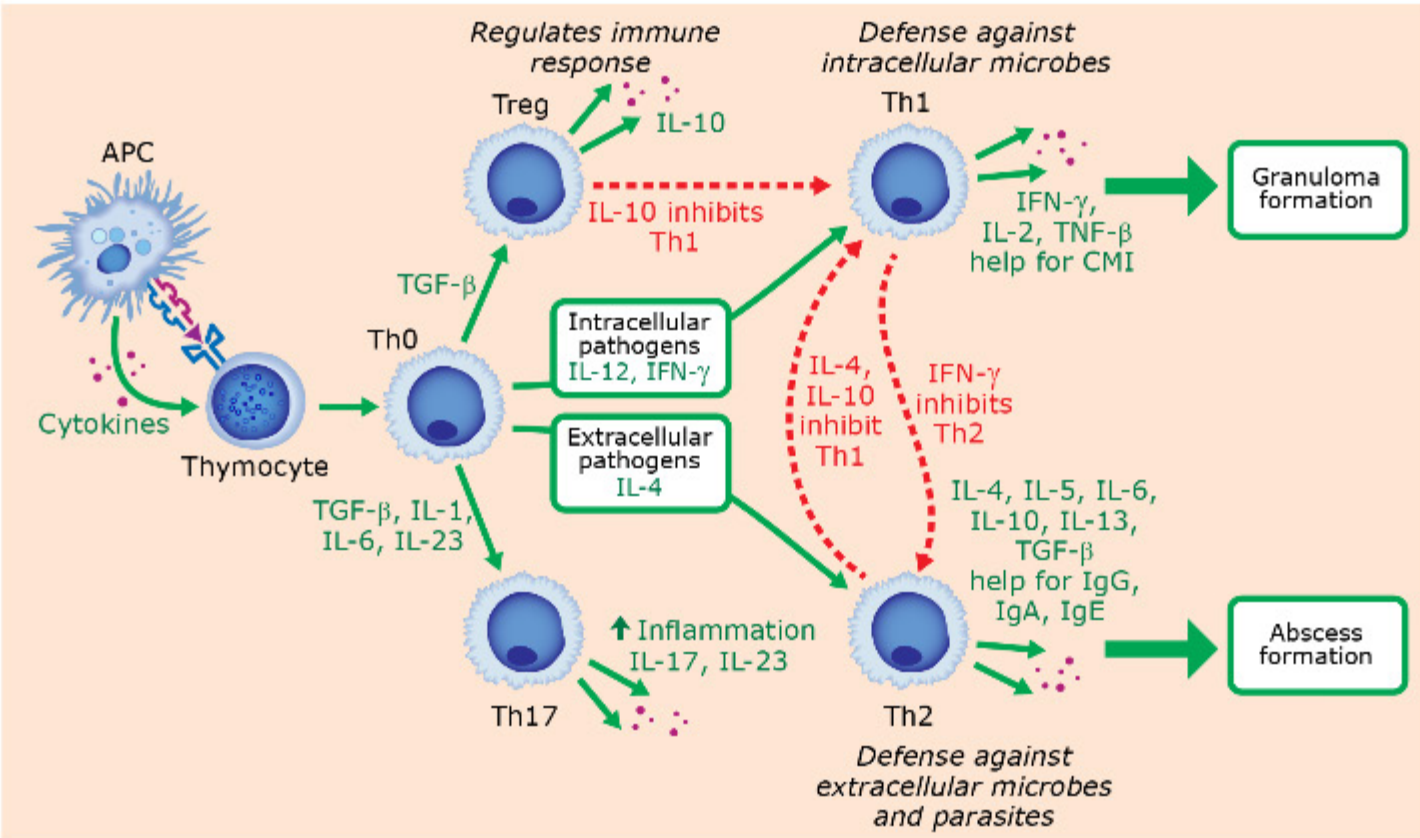
Clinical Application

Tuberculoid vs. Lepromatous Leprosy

Leprosy is a clinical spectrum of disease caused by infection with the intracellular bacterium, *Mycobacterium leprae*. The correct immunological response to a pathogen that lives inside phagocytic cells in skin and near nerves is to activate macrophages with Th1 cytokines like IFN-γ to kill the pathogen intracellularly. The patient who follows this course develops the *tuberculoid* form of the disease, which presents with few lesions and a relatively benign course. The patient whose immune system makes the wrong immunological choice will turn on Th2 cells. This response leads to *lepromatous* leprosy. As expected, these patients develop hypergammaglobulinemia, and because antibodies have no effect on bacteria inside cells, this patient will develop infections with dissemination, widespread disfigurement, and up to 10^{10} acid-fast bacilli/g of tissue.

Connection to Pathology

The initial immunological decision to activate CMI or HI is a crucial one that affects an infection's ultimate pathological outcome. Chronic stimulation of CMI culminates in the production of *granuloma formation*, whereas chronic stimulation of HI tends to result in *abscess formation*.



▲ **Figure 5-6.0B** Th Subpopulations

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Review Questions Chapters 3–5

1. A 12-month-old child is referred to a specialist because of recurrent bacterial infections and failure to thrive. A lymph node biopsy reveals the absence of germinal centers. Which of the following markers is likely to be absent from peripheral blood leukocytes in this child?

A. CD3
B. CD4
C. CD8
D. CD14
E. CD19

2. A 2-year-old child who has suffered recurrent bacterial infections and delayed wound healing is evaluated for immunologic deficiency. Numbers of CD19+ and CD3+ cells in the peripheral blood are within normal limits but neutrophil counts are elevated to almost twice normal values. Intracellular digestion is normal. What is the most likely defect in this child?

A. Addressin
B. CD18
C. Chemokine receptors
D. E-selectin
E. L-selectin

3. A 12-month-old child is referred to a specialist because of a history of repeated bacterial infections. When the child's peripheral blood leukocytes are incubated with opsonized bacteria, the production of oxygen and halide radicals was reduced compared to normal controls. What is the most likely defect in this child?

A. Catalase
B. Lactoferrin
C. Myeloperoxidase
D. NADPH oxidase
E. Superoxide dismutase

4. Endothelial cells in areas of inflammation increase expression of E-selectins in response to injury. The increased expression of E-selectins results directly in which of the following neutrophil functions?

A. Activation
B. Adherence
C. Chemotaxis
D. Demargination
E. Rolling
F. Transmigration

5. Radiolabeled autologous neutrophils are injected intravenously into a patient with an occult bacterial infection, and this treatment is followed by whole-body scintigraphy. Which of the following molecules will be found in the highest concentration in areas with elevated radioactive signal?

A. Interleukin-1
B. C3b
C. C5a
D. Hageman factor
E. Prostaglandin

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Chapters 3–5 Review Questions

6. A 60-year-old woman is admitted to the hospital with sudden onset of fever, left-sided chest pain, and labored breathing. On auscultation there is evidence of pleural effusion. Which of the following is most likely to characterize the histologic appearance of the lung?

A. Angiogenesis, fibroblasts, proteoglycans
B. Collagen, fibroblasts, contraction
C. Lymphocytes, macrophages, antibodies
D. Mast cells, histamine, vasoconstriction
E. Neutrophils, vascular congestion, edema

7. An outbreak of parainfluenza virus in a nursing home necessitates hospitalization for several affected residents. The patients with more severe disease were observed to be making high amounts of interleukins 4, 5, 6, and 10. What cell is responsible for this pattern of interleukin production?

A. Macrophage
B. Natural killer cell
C. Th1 lymphocyte
D. Th2 lymphocyte
E. Th17 lymphocyte
F. Treg lymphocyte

8. A 64-year-old man complains of difficulty breathing and a productive cough. Physical examination yields a fever and blood-tinged sputum containing acid-fast bacilli. X-ray analysis reveals several opacities in the upper lobe of the left lung. Needle biopsy of one of these masses reveals lymphocytes and activated macrophages. Which of the following cytokines is most strongly associated with the formation of this lesion?

A. Interferon-α
B. Interferon-γ
C. Interleukin-1
D. Interleukin-2
E. Tumor necrosis factor-α

9. One of the drugs used to treat multiple sclerosis is glatiramer acetate. Its mechanism of action is thought to involve a switch in T cell response from a proinflammatory to an anti-inflammatory response. If this is true, which of the following cytokines would be found in the serum of a patient who has been taking this drug for several months?

A. IFN-γ
B. IL-1
C. IL-10
D. IL-12
E. TNF-α

10. Transgenic mice are generated that are incapable of expressing MHC invariant chain. Which of the following components of host defense is most likely to be altered in these mice?

A. Immunoglobulin M synthesis
B. Cytotoxic T lymphocytes
C. Interleukin-2 (IL-2) secretion
D. Natural killer cells
E. Antibody-dependent cell-mediated cytotoxicity (ADCC)

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Review Answers Chapters 3–5

1. The correct answer is E. Germinal centers are clones of dividing B lymphocytes. Therefore, if the child has no germinal centers, this is a B lymphocyte immunodeficiency, and the cell marker that is missing from the blood is the B lymphocyte signal transduction molecule, CD19.

2. The correct answer is B. This child has leukocyte adhesion deficiency-1 (LAD-1), an inability to produce the common β chain (CD18) of integrin molecules. As a result, the patient's leukocytes are incapable of extravasation, and production of abscesses or pus.

3. The correct answer is D. This child has chronic granulomatous disease, and the genetic defect is in generation of NADPH oxidase. Because all the oxygen-dependent products are deficient, the defect must be at the top of the cascade and is not simply due to myeloperoxidase deficiency, which would have made the cells deficient only in halide production.

4. The correct answer is E. E-selectins on injured endothelia bind to addressins on leukocytes, causing loose binding. This allows them to roll along the surface of the endothelium, but is not a tight enough binding to cause attachment or extravasation.

5. The correct answer is C. The material on the list that is strongly chemotactic for neutrophils is C5a. Other chemoattractants for neutrophils include fibrinopeptides, n-formyl methionyl peptides, leukotriene B4, and interleukin 8.

6. The correct answer is E. The patient is suffering from acute pneumonia and her lung should show signs of acute inflammatory change. The cardinal signs of acute inflammation are redness (from increased blood flow), swelling (from influx of inflammatory cells and increased blood flow), heat (from increased blood flow and release of pyrogenic cytokines), and pain (from activation of arachidonic acid metabolites).

7. The correct answer is D. The cell source for these cytokines is the Th2 cell. Because parainfluenza is a virus, and a syncytial one at that, recovery is strongly linked to CMI and the action of Th1 cells. So it makes sense that the patients with more severe disease are those who are making the wrong Th cell and activating a humoral immune response.

8. The correct answer is B. The patient has reactivational tuberculosis, and the lesion described is a granuloma. Granulomas result from the action of Th1 cytokines on infected macrophages, and the most important cytokine in this case is interferon-γ.

9. The correct answer is C. The cytokine on the list with anti-inflammatory characteristics is IL-10. It is a product of Th2 cells and Treg cells. It acts by inhibiting the activation of Th1 cells, which tend to be proinflammatory.

10. The correct answer is C. The invariant chain is necessary for the proper loading of MHC class 2 molecules, so in the absence of its production, Th cell activity is disrupted. Because Th cells are the only source of IL-2, and since their activation requires MHC class 2 presentation, this is the one answer for which function is most severely affected.

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1 Overview of Humoral Immunity

Humoral immunity (HI) results when B lymphocytes differentiate into plasma cells and secrete antibodies. Antibodies can be a useful protection against the binding of viruses or toxins to host cell membranes (the process of *neutralization*), or they can coat extracellular particulates to enhance phagocytosis and leukocyte degranulation, or complement activation with subsequent lysis.

2 T Cell Independent B Cell Activation

In the absence of T cell help, B lymphocytes are "stuck" making IgM and IgD, and if their BCRs become cross-linked by their cognate antigen, IgM- and IgD-producing plasma cells can be produced. However, there is no "memory" or amplification or refinement of the response in the absence of T cell help. Antigens that evoke this sort of response directly from B cells without T cell help are referred to as *T cell independent antigens*.

These molecules share a common trait: They are *devoid of protein*. Because protein is a necessary constituent of any living cell or infectious agent, there are no naturally occurring agents of infectious disease that cause B cell stimulation in a T cell independent fashion, but there are single molecular constituents that can be used as examples of this phenomenon. Since BCRs are capable of binding specifically to any type of molecule (protein, polysaccharide, lipid, and nucleic acid) they can produce antibodies against virtually anything with sufficient size and molecular complexity.

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the mechanisms of antibody production against T cell dependent and T cell independent antigens.
- Identify the basic structure and function for the five antibody isotypes.
- Describe the meaning of Fc and Fab and the role of these components in antibody function.
- Explain the meaning of avidity and affinity.
- Define how the antibody response evolves over time and stimulation.
- List the mechanisms of activation and the functions of the three complement cascades.

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Clinical Application

Allergies and Hapten–Carrier Responses

A demonstration of B and T lymphocyte cooperation to produce antibodies and what happens in the absence of such cooperation is seen during interactions with haptens and carriers.

Haptens are antigens that do not have the size and molecular complexity to cause lymphocyte activation. This is because they are single epitopes (structures complementary to the idiotype of the cell's antigen receptor) without the capacity to cross-link those receptors or cause stimulation of signal transduction.

Many drugs such as aspirin, opiates, penicillin, streptomycin, succinylcholine, and sulfa drugs are low-molecular-weight compounds that act as haptens in the body. When therapy with these drugs is continued, however, the drug haptens can become covalently coupled to host cell membranes and elicit damaging allergic or even anaphylactic reactions. The cell then plays the role of the *protein carrier* for the hapten, and since protein content is essential for development of a T cell dependent antigen, the combination of *hapten-carrier* delivers all the molecular necessities for T cell dependent activation. The BCR binds the haptenic moieties, and the TCR recognizes the cellular peptides presented in MHC class 2 molecules. This results in the production of an immune response that destroys the haptenated host cells. Other haptens that elicit similar hypersensitivity reactions include nickel (in inexpensive jewelry) and the oils of *poison ivy* and *poison oak*.

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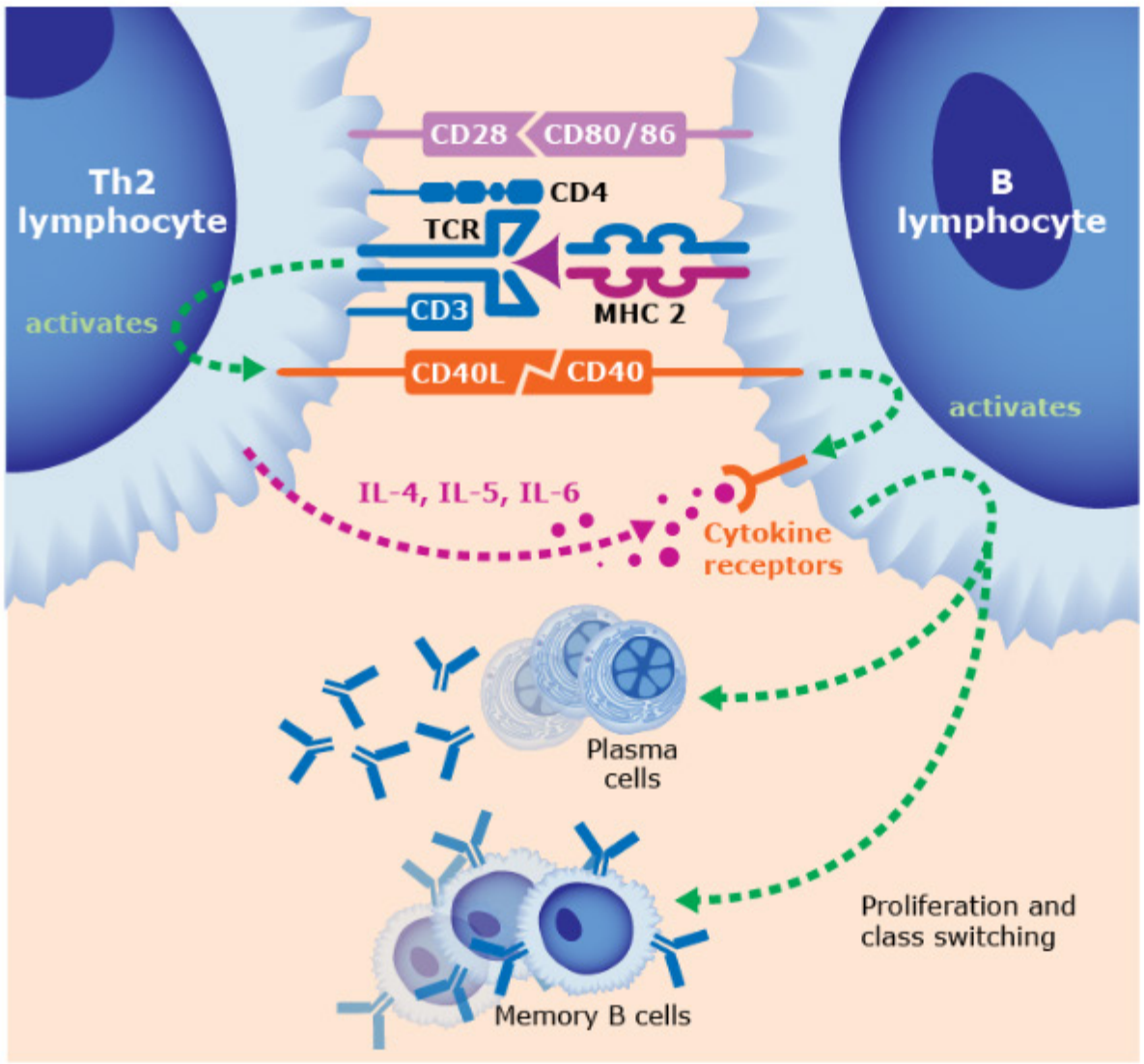
3 T Cell Dependent B Cell Activation

When a foreign substance contains protein, as do all infectious disease agents, T cell help becomes possible, and the B cell is activated to produce its full repertoire of responses. Much as is seen with the initial interaction between Th0 cells and APCs, the interaction between Th0 or Th2 cells and B lymphocytes requires three signals:

1. *Antigen-specific binding* between B cell MHC class 2/peptide complex and the TCR.
2. *Binding of costimulatory molecules* between the Th and B cell membranes.
3. Synthesis of *cytokines* by the Th2 cell to activate B cell differentiation and cloning.



▲ **Figure 6-3.0** T Cell Dependent B Cell Activation

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4 Class Switching

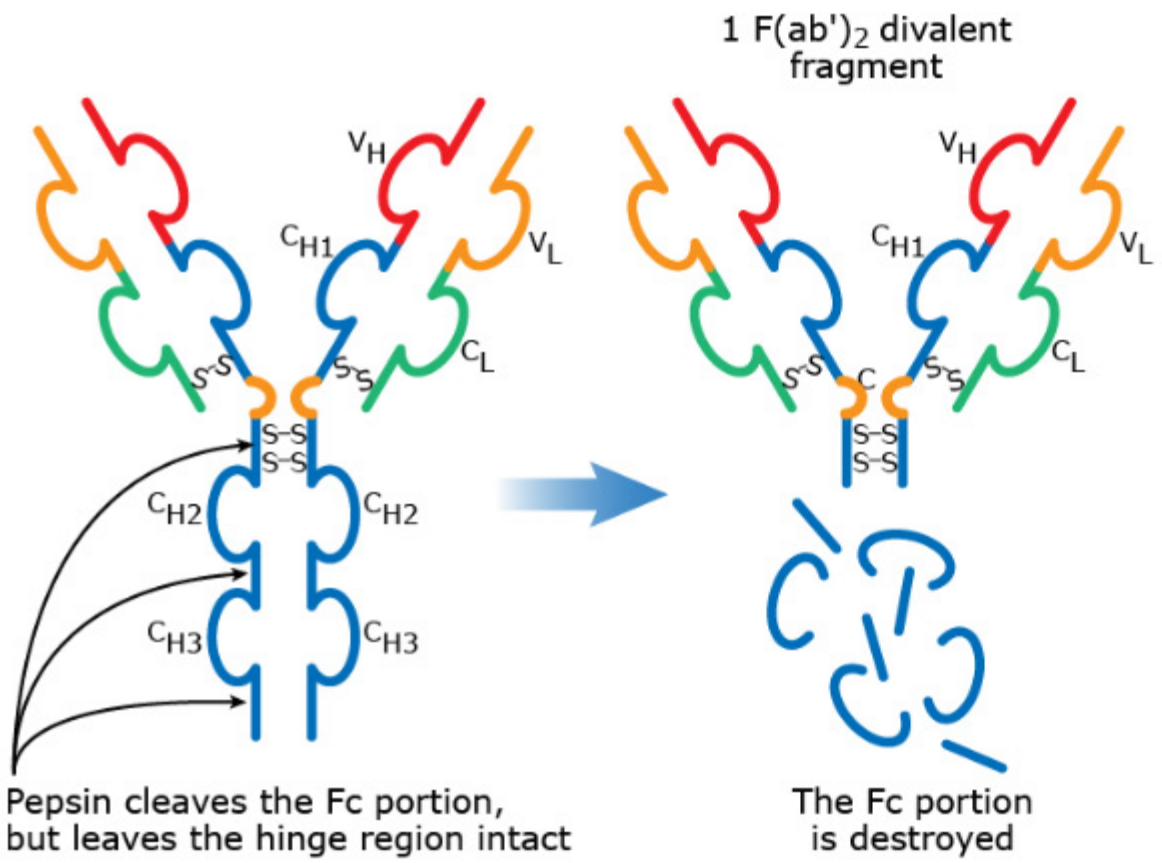
The cytokines secreted by activated Th2 cells cause B lymphocyte cloning, isotype switching, and differentiation into plasma cells:

- B lymphocyte cloning produces the number of antigen-specific effector cells necessary for the destruction of the invader.
- Isotype switching changes the function of the antibody molecule by changing the expression of the constant domains of the molecule.
- Differentiation into plasma cells provides a short-lived factory for antibody synthesis so that the maximum amount of the protective protein can be pumped out into the circulation.

4.1 Proteolytic Cleavage of Immunoglobulin

Early immunologists discovered the function of the anatomical pieces of the immunoglobulin molecule by artificially cleaving it with digestive enzymes. There is no natural, physiological corollary to this process, but the studies determined that the N-terminal arms of the molecule were the areas that had antigenic specificity. These became known as the *Fab* (fragment, antigen-binding). The tail of the molecule was named *Fc* (fragment, crystallizable). Immunologists determined that this region was responsible for the effector functions of the molecule.

Based on what immunologists now know, we can say that *Fab contains the idiotype of the molecule*, and that the *isotype of the molecule dictates the effector functions*. For this reason, the goal of isotype switching under the influence of Th cytokines is to fine-tune the antibody's mechanism of action while keeping its antigenic specificity unchanged.



▲ **Figure 6-4.1A** Pepsin Cleavage of Ig

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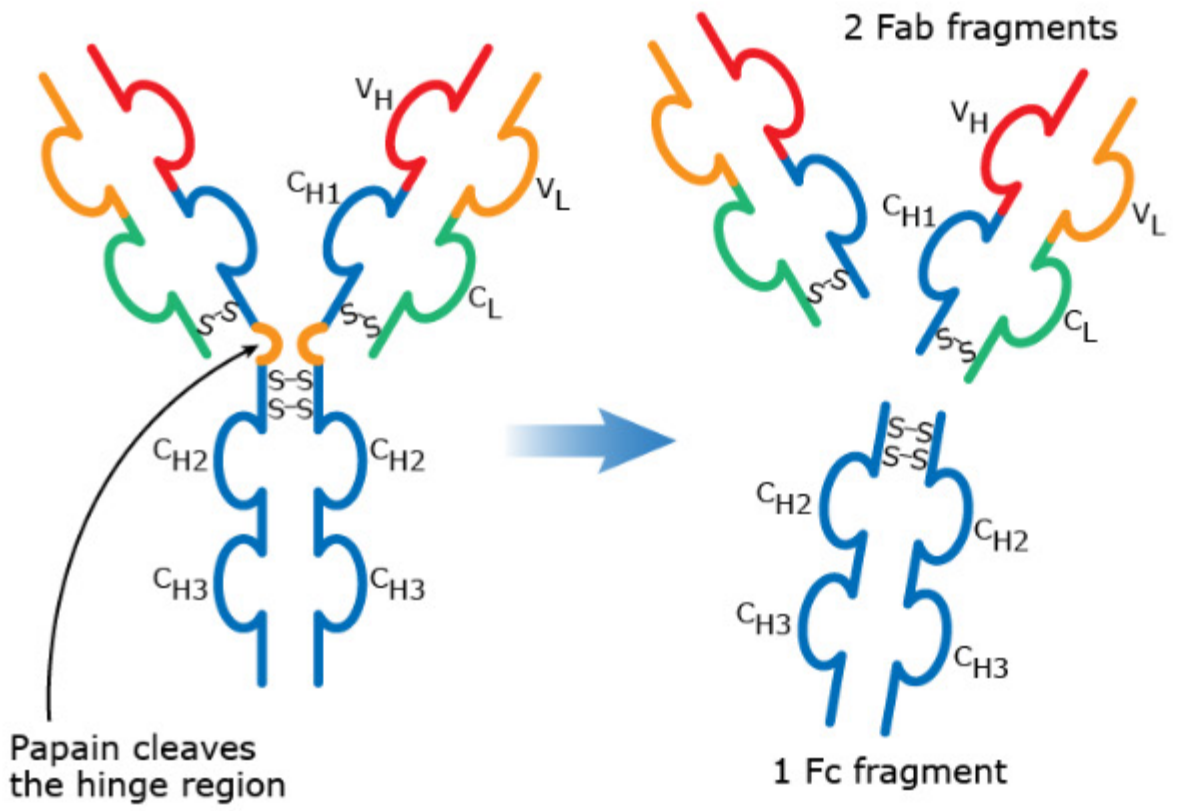

▲ **Figure 6-4.1B** Papain Cleavage of Ig

Clinical Application

Many immunological diagnostic tests depend on the visualization of the binding of antigen and antibody, a process happening at the molecular level. Precipitation and agglutination tests both depend on aggregation of such Ag/Ab complexes becoming too heavy to stay in solution or suspension. For complexes of this size to be created, two Fab fragments must remain joined together. This makes cross-linking between antigen molecules feasible. Therefore, *precipitation and agglutination can be accomplished with F(ab)'2 fragments from pepsin, but not with papain-cleaved Fab fragments.* The difference between agglutination and precipitation is merely in the nature of the antigen. *Soluble proteins become insoluble and precipitate. Particulate antigens like erythrocytes or latex beads agglutinate* when they become too heavy to remain in suspension.

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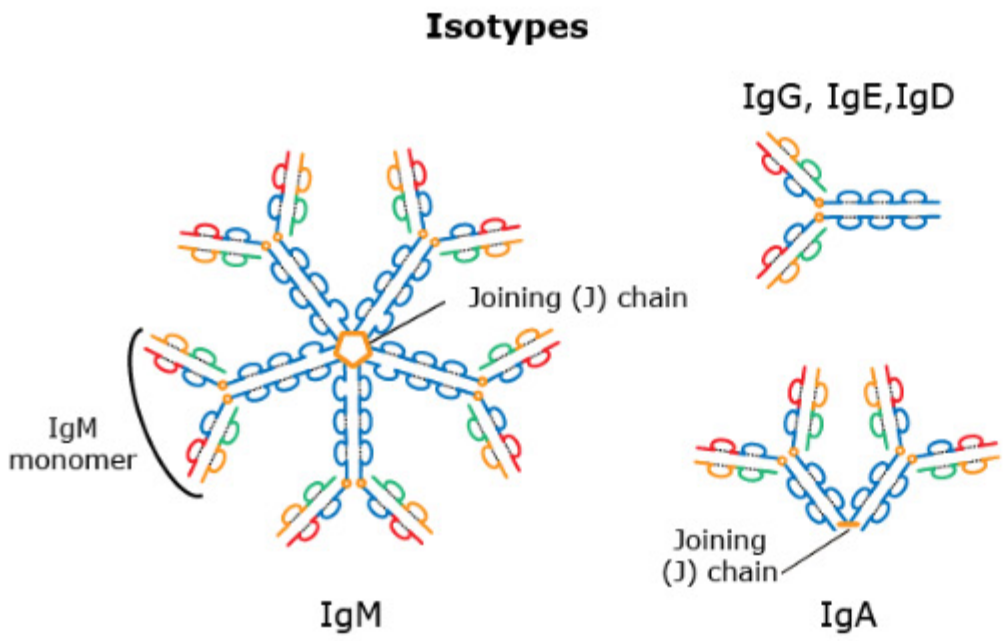
4.2 Structure and Function of IgM

The first immunoglobulin made by a B lymphocyte is IgM. It and IgD (whose function is unknown) are the only antibodies that can be produced in the absence of T cell help.

4.2.1 Structure

The IgM found in the plasma exists as a *pentamer*, with five identical *monomer* units held together by a single joining chain, and its functions are ideally suited for its role as a first responder. It has the largest number of combining sites of any antibody produced.



▲ **Figure 6-4.2** IgM Structure

4.2.2 Function

- The structure of IgM allows it to work like an immunological sponge, capturing antigen and trapping it in a secondary lymphoid organ for subsequent immune stimulation.
- The IgM pentamer has a valence of 10, meaning that it has 10 identical idiotypes to bind to its antigen.
- IgM is the strongest activator of complement produced, and this serves to enhance inflammation and attract more immune cells into the area.
- IgM cannot act as an opsonin, since this would require a free Fc tail to fit the CD16 receptor on a phagocyte, and the internal structure of this pentamer is much too sterically hindered.

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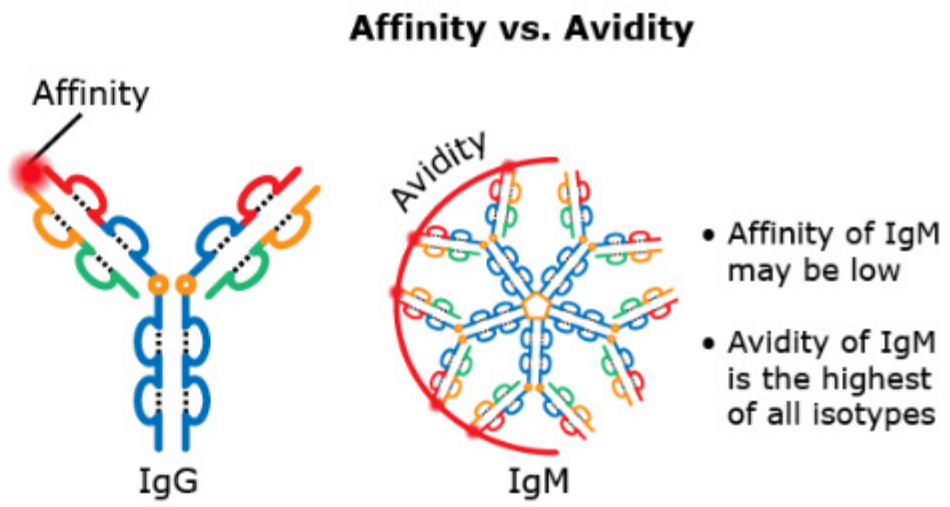
5 Affinity Maturation

As the B lymphocyte interacts with a Th2 cell, the Th2 cell delivers a signal that causes the B cell to change the isotype of antibody that it is producing. By definition, then, the new antibodies produced will have a lower valence, because IgM has the highest number of combining sites of any isotype.

To make up for this loss of valence, all subsequent antibodies have refinements of the goodness-of-fit of their idiotypes that increase the *affinity* of their antibodies.

5.1 Affinity vs. Avidity

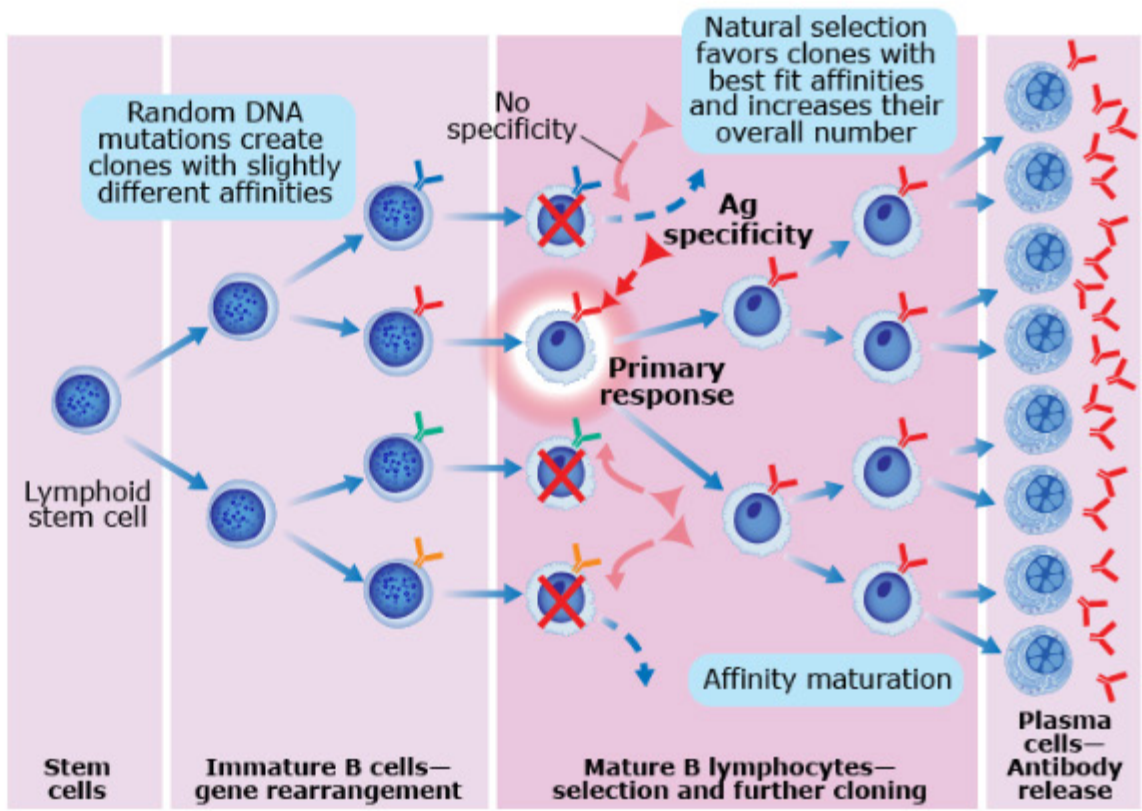
The compromise that is made between *avidity* (the number of combining sites available for binding) and *affinity* (the measure of the one-to-one goodness-of-fit of a single idiotype for its epitope) is classic in biological systems. As a B cell undergoes isotype switching to produce an immunoglobulin other than IgM, the avidity of antibody populations will decrease. This problem, however, is offset by mutational changes to the idiotype domains which will increase antibody affinity overall.



▲ **Figure 6-5.1** Affinity vs. Avidity

5.2 Somatic Hypermutation

The modification of the shape of the idiotype of antibodies occurs during the burst of clonal proliferation engendered by Th2 cytokines. As B lymphocytes undergo *blastogenesis*, random mutations within the DNA coding for the variable domains (*somatic hypermutation*) creates subpopulations of B cells, each clone with slightly different affinity for the original antigen. *Natural selection* between these clones for the best fit of BCR causes the overall population of secreted antibodies to increase in affinity, with each administration of antigen in a process referred to as *affinity maturation*.



▲ **Figure 6-5.2** Clonal Selection of B Cells

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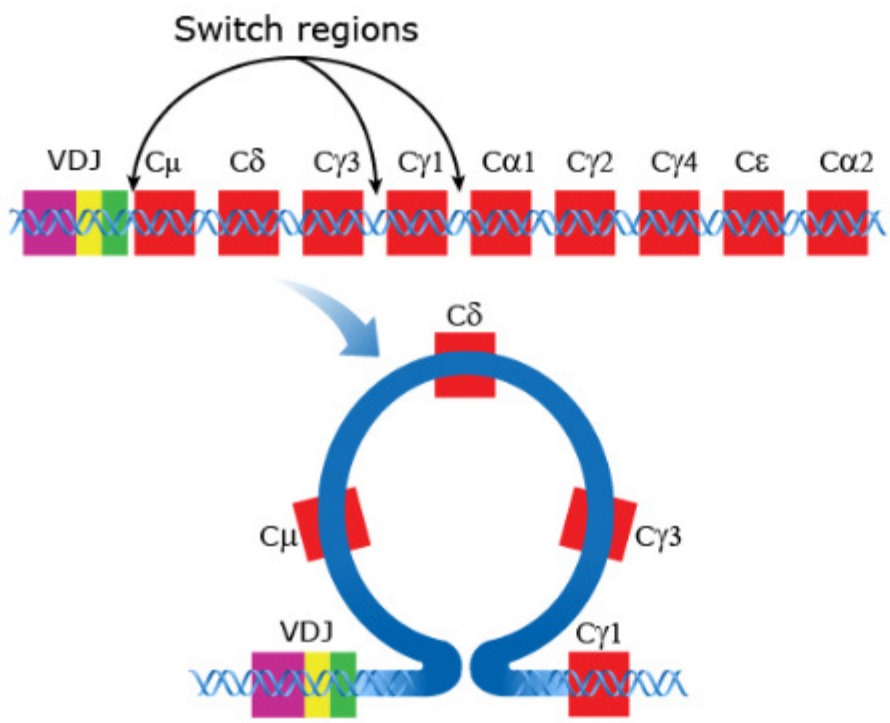
6 Isotype Switching

Isotype switching changes the function of the antibody molecule by changing the expression of the molecule's constant domains. Because the isotype of the molecule dictates its ultimate effector function, this is the body's way of developing the specific killing mechanism most appropriate for a given invader.

6.1 Germline DNA Rearrangements

Under the influence of specific Th2 cytokines, switch regions found in the germline DNA of B lymphocytes are activated, and the intervening DNA is looped up, excised, and degraded. This joins the original VDJ (idiotype) coding to a new set of constant domains and changes the effector function of the antibody being produced. The switching is unidirectional and irrevocable. A cell that has switched from its primary response (IgM and IgD) can never go back to making those isotypes again. The cytokine signals can be quite complex and mixed, but two cytokines have clear association to particular switch regions:

- IL-5 causes switch to IgA synthesis.
- IL-4 causes switch to IgE synthesis.



▲ **Figure 6-6.1** Germline DNA Rearrangements

6.2 Structure and Function of IgG

Because there are four possible switch regions for IgG subisotypes, it is a statistical probability that the first immunoglobulin produced after IgM is IgG. IgG has the greatest number of effector functions:

- Complement activation
- Opsonization
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Active transport across the placenta

Memory Aid

The most testable isotype switch cytokines:

5-Always and **4-E**ver
(IL-5 produces IgA and IL-4 produces IgE.)

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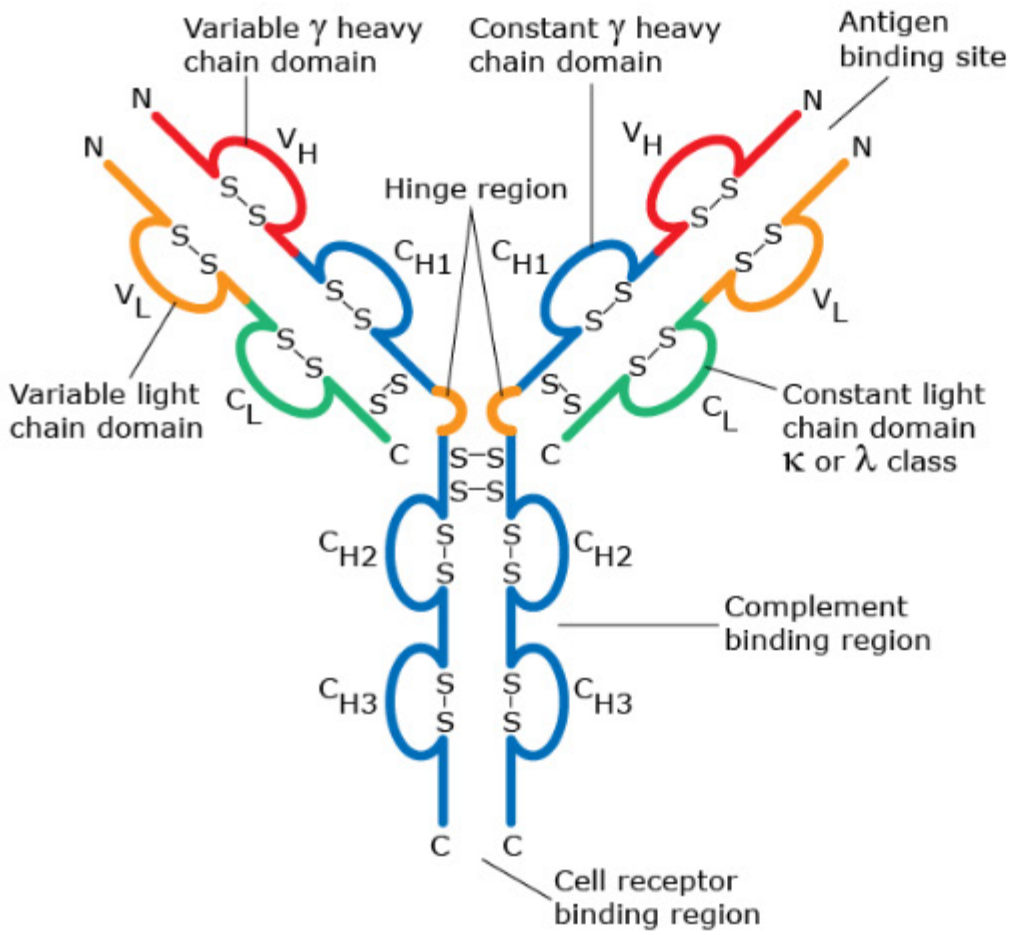
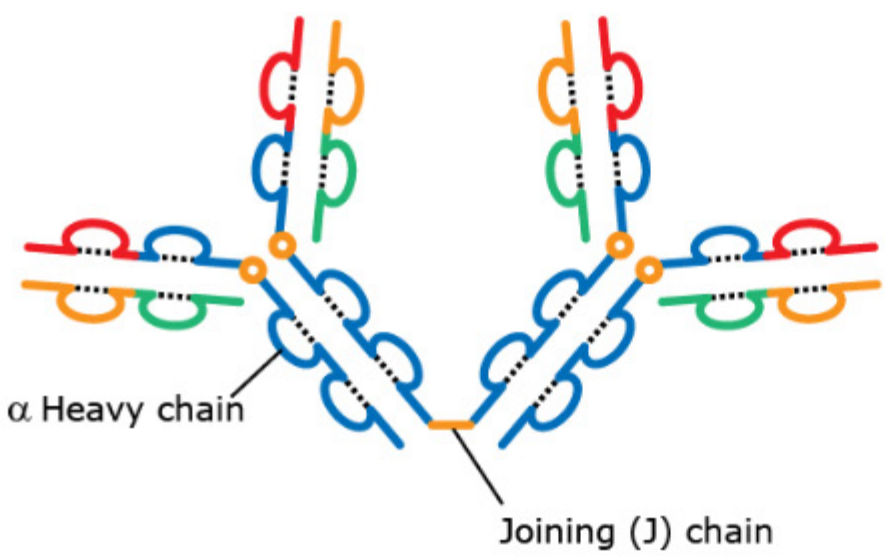


▲ **Figure 6-6.2** IgG Structure

6.3 Structure and Function of IgA

There are two possible switch regions encoding IgA synthesis, so it is usually the next choice beyond IgG. It exists as a dimer, being held together by a J-chain like that of IgM. It is the major defense of the mucosal surfaces, but has no effector functions other than neutralization or blocking of binding.

IgA does not act as an opsonin, nor does it activate complement. It is the major immunological component of breast milk and colostrum, passively protecting the mucosal surfaces of the neonate from pathogens that try to adhere there.



▲ **Figure 6-6.3A** IgA Structure

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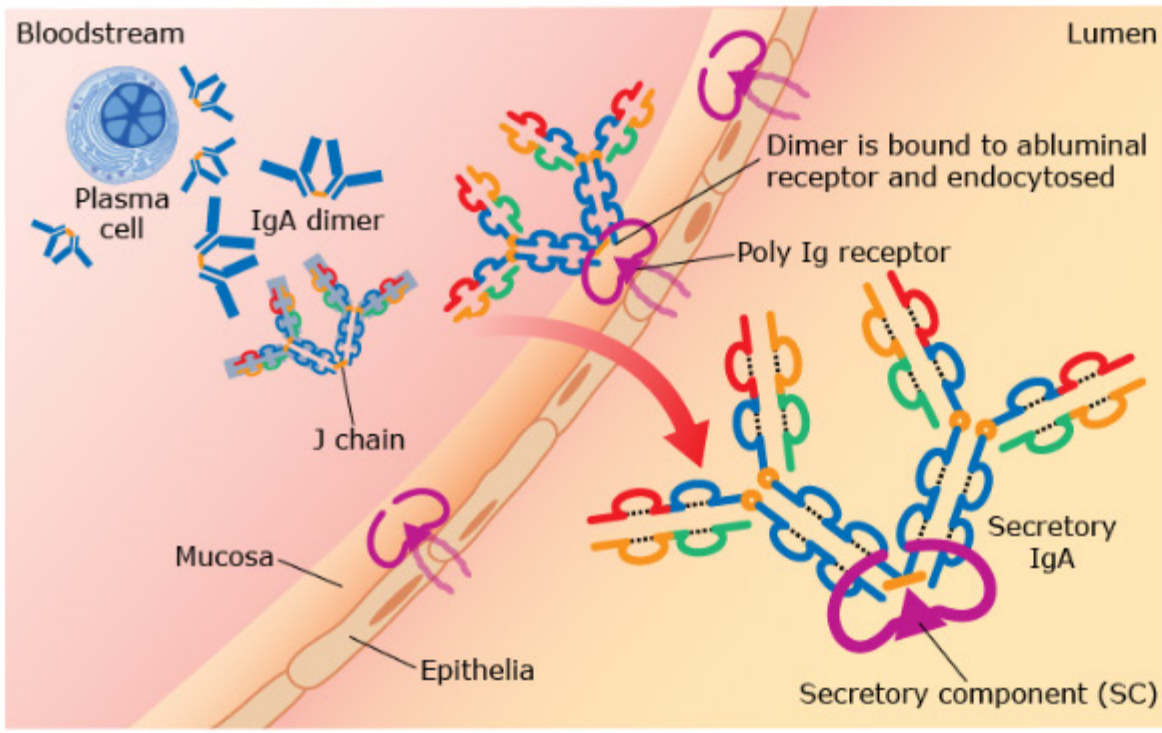
As IgA is produced by plasma cells in the submucosa, it binds to poly-IgA receptors on the internal surface of the epithelium. This binding causes the antibody to be endocytosed by the epithelial cell and transported to the luminal side of the mucosa, where it is released. The residue of the poly-IgA receptor, now called a *secretory component*, covers the bond-rich regions of the molecule and protects them from proteolytic cleavage in the gastrointestinal, respiratory, or urogenital systems.



▲ **Figure 6-6.3B** Secretory IgA

IgE is nature's last choice of antibody synthesis because of its extremely damaging attributes. It is a monomer and binds to specialized Fc receptors (FcRε) found on mast cells and basophils. It is a portion of the protective immune response against helminth parasites, but when it is misdirected, the misery of atopic allergy results.

▼ **Table 6-6.3** Antibody Isotype Functions

	IgM	IgD	IgG	IgA	IgE
Heavy chain	μ	δ	γ	α	ε
Serum level (mg/dL)	45–250	trace	620–1420	80–350	trace
Naive B cell receptor	+	+	–	–	–
Memory B cell receptor (one only)	–	–	+	or +	or +
Classical complement activation	+	–	+	–	–
Opsonization	–	–	+	–	–
ADCC	–	–	+	–	–
Crosses placenta	–	–	+	–	–
Mast cell degranulation	–	–	–	–	+

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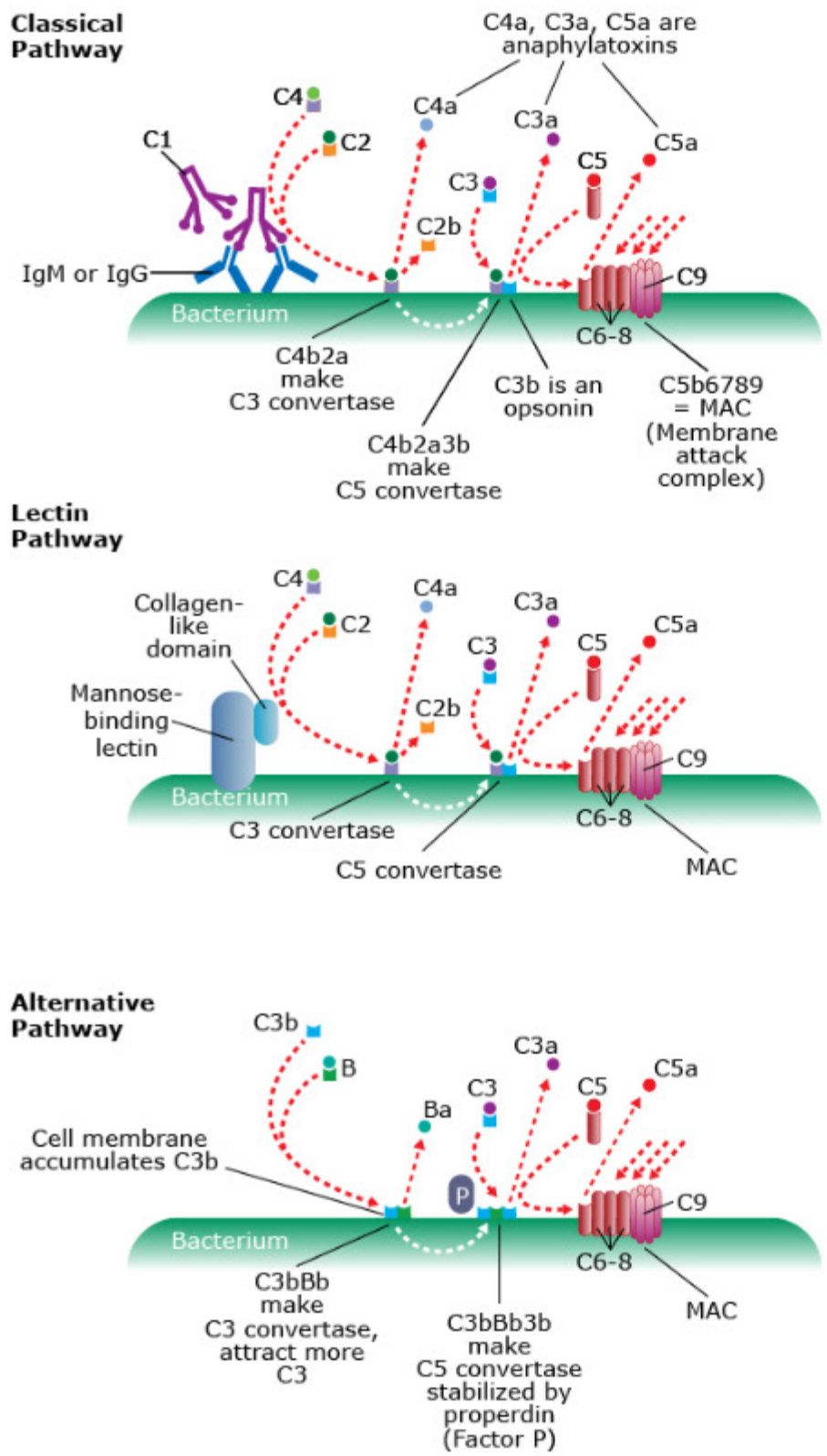
7 Complement

The complement system is a set of proteins found in the blood and produced in the liver. They act on each other in a cascading fashion reminiscent of the clotting cascade, and culminate in the destruction of the membrane of the cell to which they adhere.

7.1 Alternative, Classical, and Lectin Pathways

There are three mechanisms of complement activation. The classical cascade requires IgM or at least two molecules of IgG bound to the surface of a target cell. The alternative cascade is begun by recognition of microbial polysaccharides or lipopolysaccharides. The lectin cascade uses mannose-binding lectin to bind bacterial carbohydrates.



▲ **Figure 6-7.1** Alternative, Classical, and Lectin Pathways

Clinical Application

Patients with immune complex hypersensitivities (type III) often develop complement deficiencies because of the overactivation of complement to deal with these antigen-antibody complexes.

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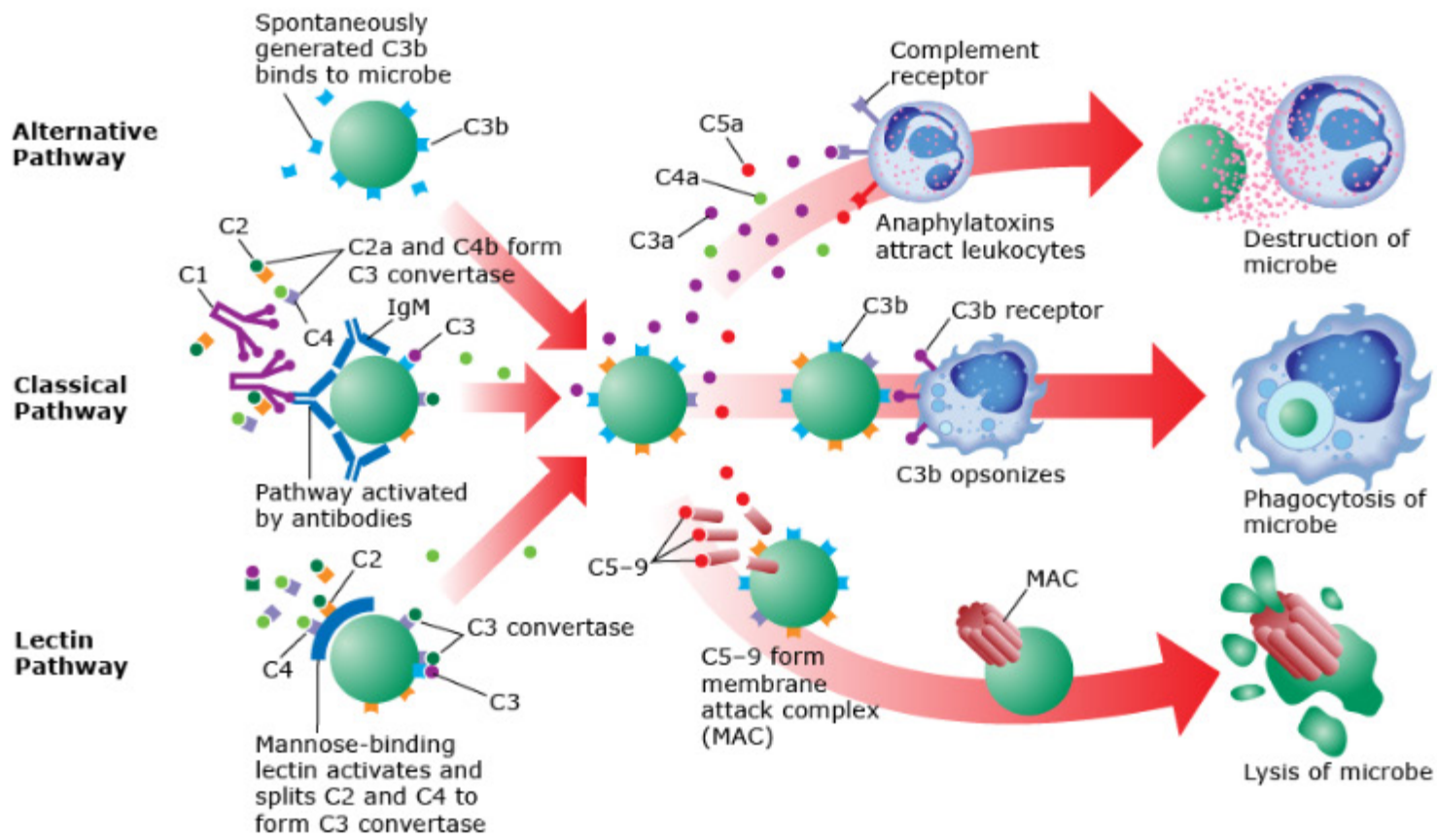
7.2 Functions of Complement Split Products

As each of these cascades is initiated, split products are generated that have important roles in promoting cellular infiltration and opsonization. C3a, C4a, and C5a are called *anaphylatoxins* because of their ability to recruit inflammatory cells. C3b is an important *opsonin*, coating particles to enhance phagocytosis. It is also important for the clearance of immune complexes from the blood. Components 5 to 9 are collectively called the *membrane attack complex* because they cause the production of holes in cellular membranes.



▲ **Figure 6-7.2A** Complement Split Products

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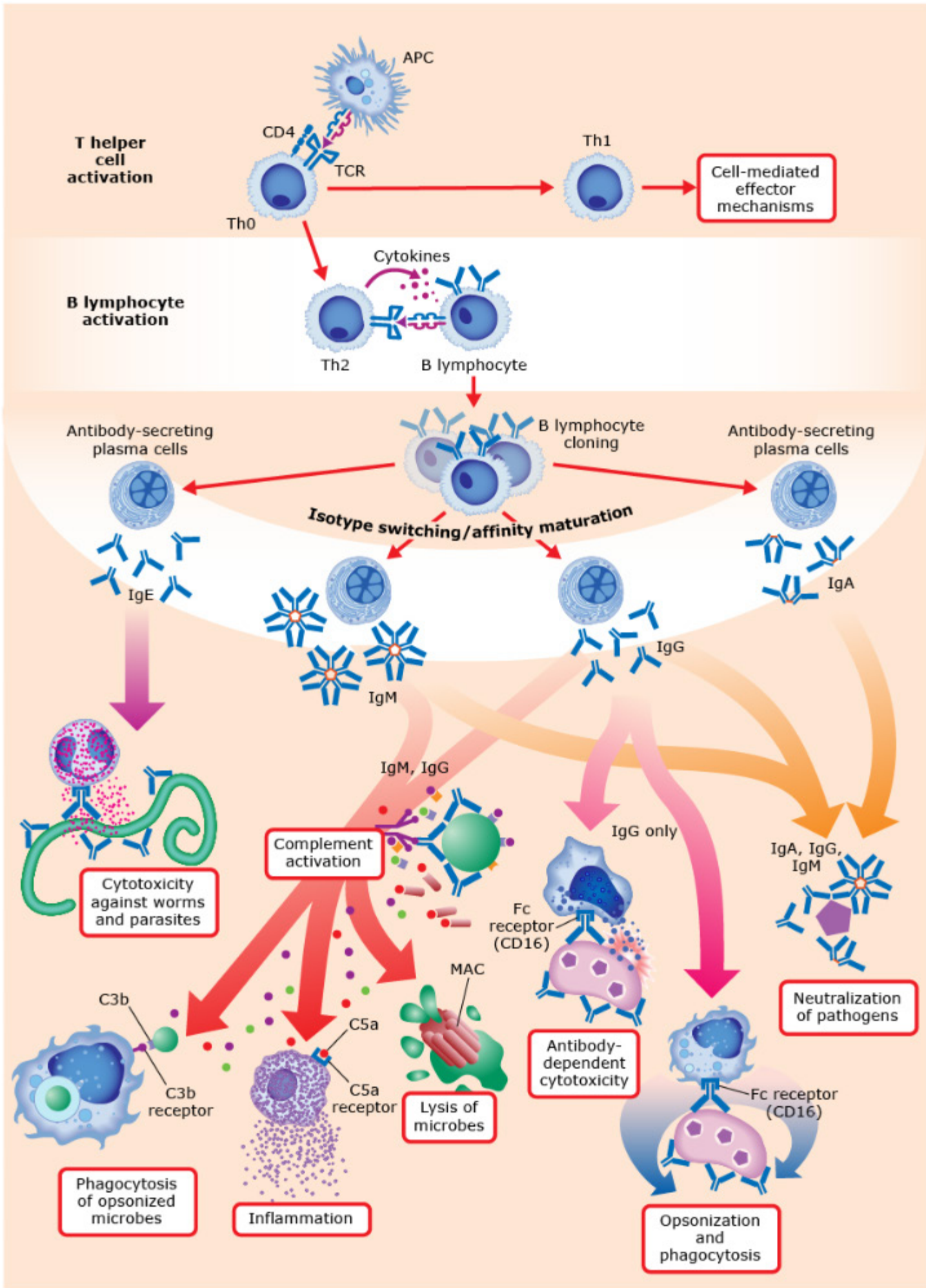

▲ **Figure 6-7.2B** Summary of Humoral Immunity

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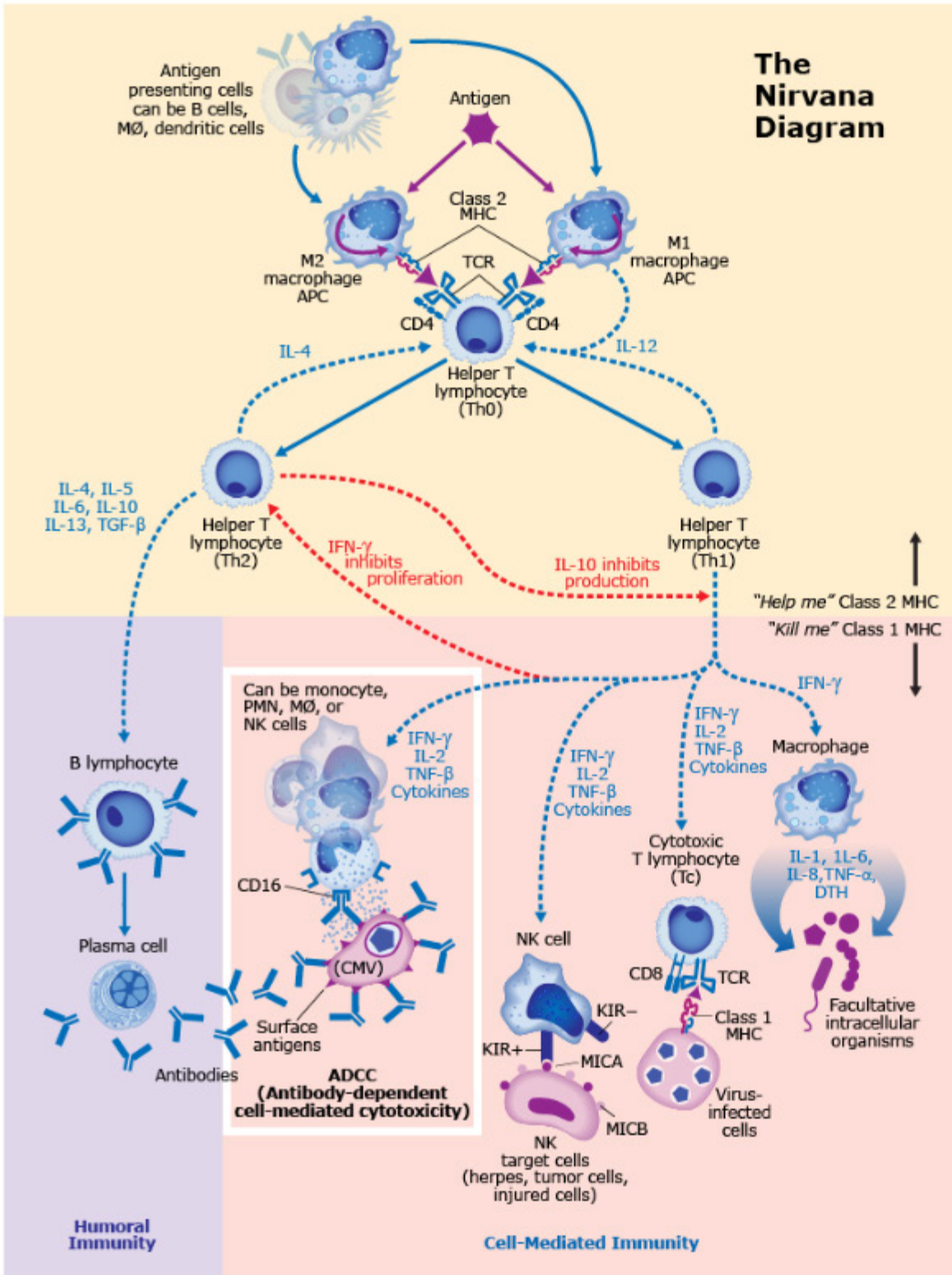
1 Overview of Cell-Mediated Immunity

When cells of the body become abnormal, either by the presence of an intracellular-dwelling microbe or by a process of malignant transformation, the arm of adaptive immunity that must rise to the challenge is the cell-mediated immune (CMI) response. This arm of the immune response is controlled by the Th1 lymphocyte and its cytokines, and the immune cells that target the altered host cells for killing (the *effector cells*) are specially evolved to combat pathogens of different kinds.



◀ **Figure 7-1.0** Nirvana

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the biological purpose and means of activation of cell-mediated immunity.
- Identify the mechanisms of effector cell killing and the disease settings in which they would be used.

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2 Effector Cells of CMI

The effector cells controlled by the Th1 include macrophages, cytotoxic T lymphocytes (Tc), natural killer (NK) cells, and leukocytes capable of performing antibody-dependent cell-mediated cytotoxicity (ADCC).

2.1 Macrophages

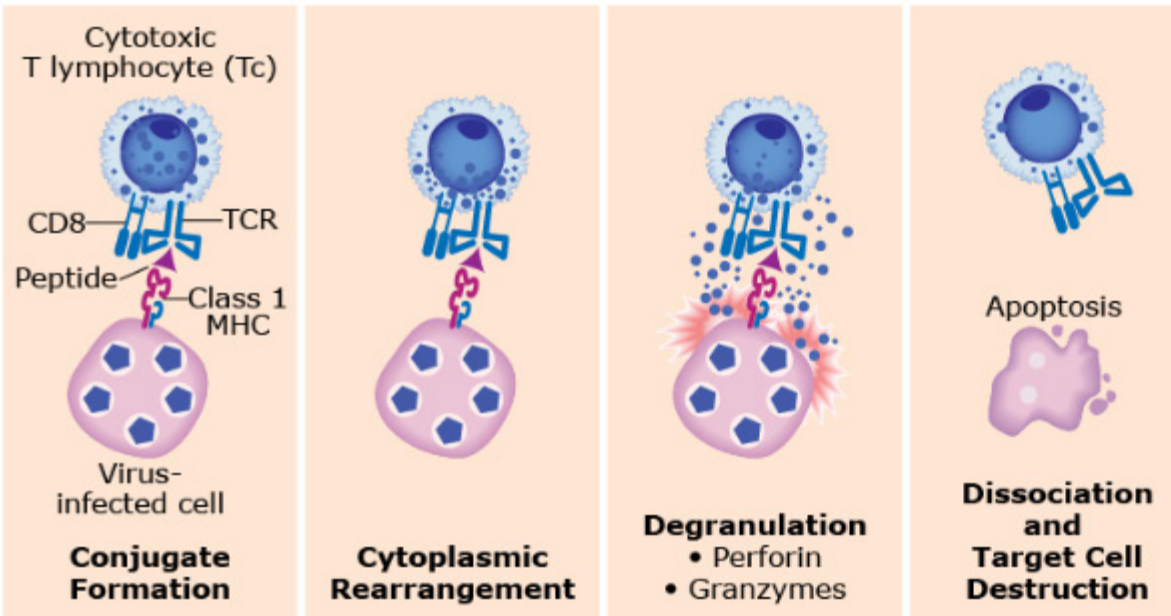
Macrophages are the only cell of CMI that kills its enemy intracellularly following phagocytosis. Although phagocytosis is an innate ability of macrophages, when these cells are bathed in the cytokines of Th1 cells, and in particular, interferon-γ, they become more aggressive and effective killers. Macrophages are the preferred effector cell, then, when the microbe is a *facultative intracellular organism*, or one that survives inside phagocytes after being ingested.

2.2 Cytotoxic T Lymphocytes

The cytotoxic T cell (Tc) is tasked with killing altered host cells expressing abnormal peptides in the groove of their MHC class 1 molecules. This effector cell of the CMI is therefore the major protective effector against viruses and other *obligate intracellular microbes*. Tc can also kill tumor cells as long as they express MHC class 1 molecules, but often tumor de-differentiation causes a loss of these molecules, and such tumor cells become refractory to Tc killing.

Tc kill their targets extracellularly, by delivering toxic granule contents through channels produced in the target cell membrane. This is a four-step process that can be repeated again and again by a single Tc:

1. **Attachment** to the target (TCR, CD8, integrins)
2. **Cytoskeletal rearrangement**
3. **Exocytosis of granules** (perforin and granzymes)
4. **Detachment** from the target and target apoptosis via activation of caspases



▲ **Figure 7-2.2** Cytotoxic T Lymphocytes

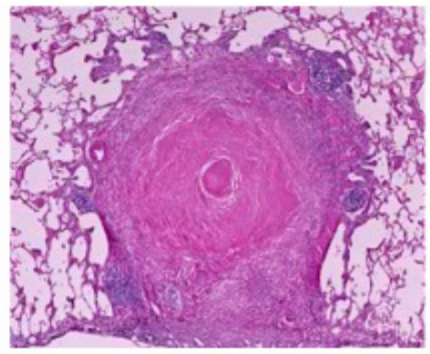
Connection to Microbiology

The medically important facultative intracellular pathogens are a fairly short list:

- *Francisella tularensis*
- *Listeria monocytogenes*
- *Mycobacterium* spp.
- *Brucella* spp.
- *Salmonella enterica* subsp. *typhi*
- *Legionella pneumophila*
- *Yersinia pestis*
- *Nocardia* spp.
- *Histoplasma capsulatum*
- *Leishmania* spp.

Connection to Pathology

The classic demonstration of chronic activation of this effector system of CMI is the development of *granulomas*. Granulomas are spherical accumulations of Th1 lymphocytes and activated macrophages *(epithelioid cells)*. Macrophages that are frustrated by their inability to efficiently kill an ingested microbe become highly secretory, calling for more Th1 cell help. By contrast, neutrophils explode when frustrated in the act of phagocytosis. Accumulations of dead and dying, frustrated neutrophils produce abscesses.



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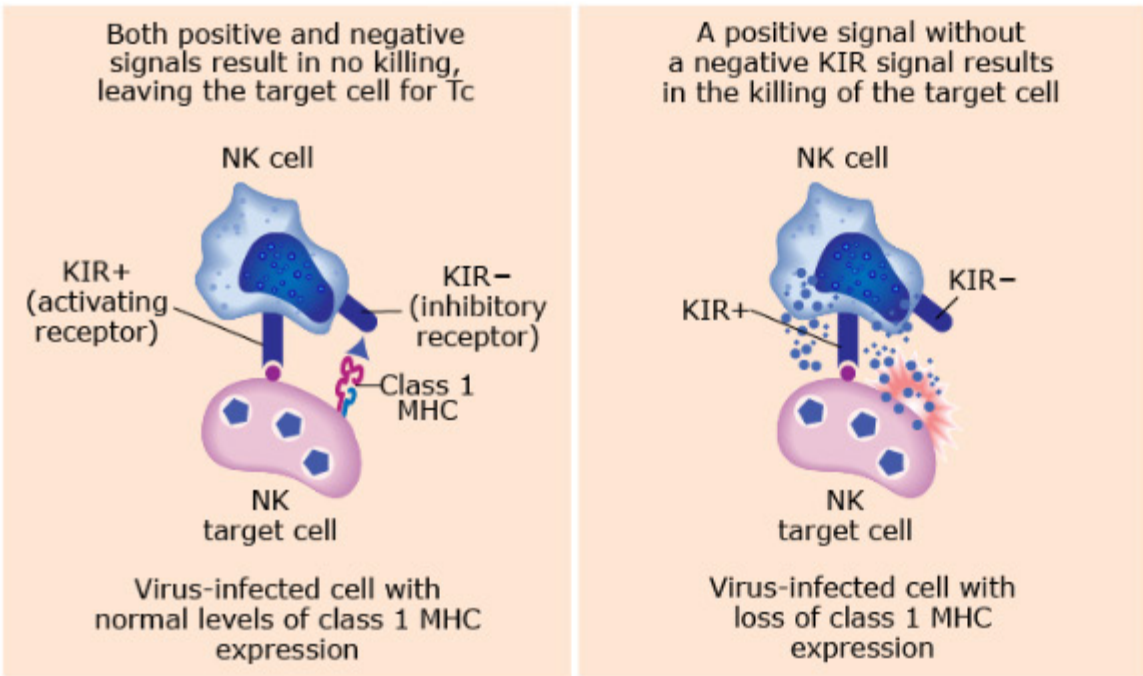
2.3 Natural Killer Cells

NK cells are the specialized effectors for those cases in which the target cell is no longer expressing MHC class 1 molecules. This happens during herpes (and other) virus infections and in many malignancies. Of course, if an infected cell does not express MHC, it cannot be targeted for killing with a Tc.

NK cells are the only lymphocytes classified as innate in their action because their stimulation does not generate memory. These cells lack the normal membrane markers of B or T lymphocytes, and are instead counted by their membrane markers, CD16 and CD56.

NK cells use two categories of receptors. Both receptors belong to the *Killer Immunoglobulin-like Receptor (KIR)* family. The activating receptor binds to lectins conserved among many groups of pathogens. The inhibitory receptor binds to MHC class 1 antigens. Thus, the NK cell steps in and targets for killing any injured or infected cell that cannot be killed by Tc because of the failure to express MHC class 1.



▲ **Figure 7-2.3** Natural Killer Cells

Connection to Microbiology

Obligate intracellular microbes are incapable of living outside of host cells. They include:

- All viruses
- Chlamydiaceae
- *Mycobacterium leprae*
- Rickettsiae
- Sporozoan parasites *(Plasmodium, Toxoplasma, Isospora, Cryptosporidium, Babesia)*
- *Leishmania* spp.

Connection to Pathology

When there is too much activation of CMI over long periods of time, damage can be caused. Excessive activity of macrophages or Tc can result in the production of type IV (delayed-type) hypersensitivity reactions.

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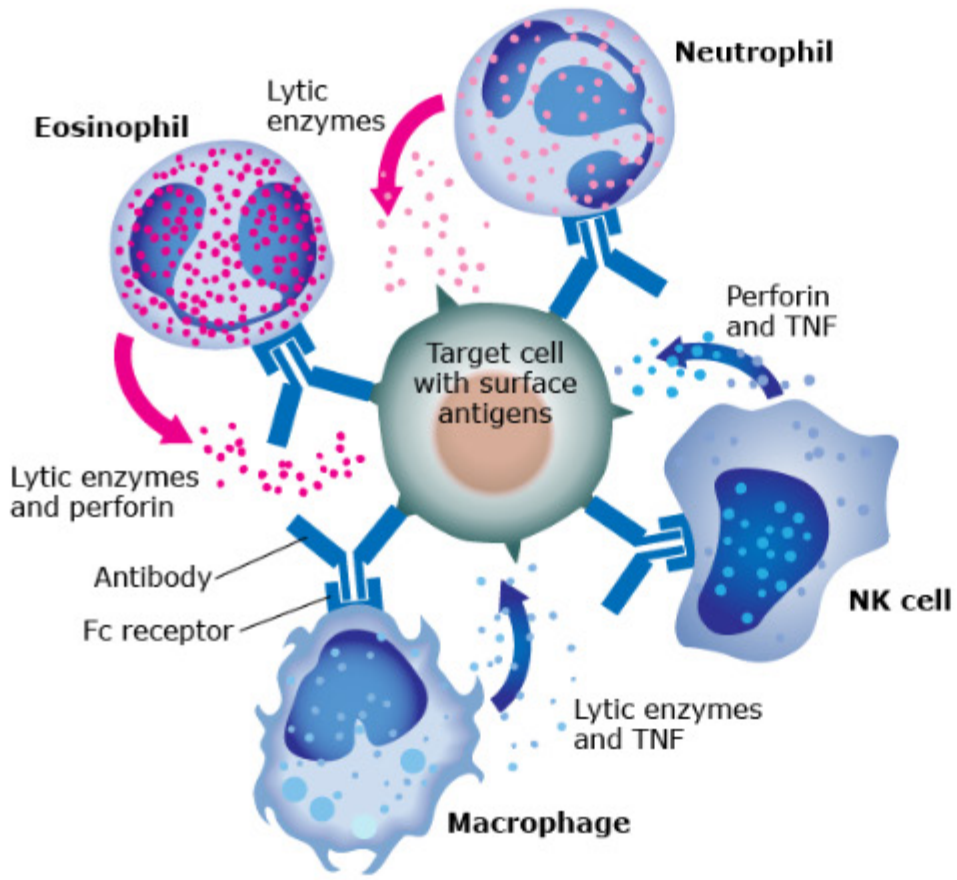
2.4 Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)

The final effector mechanism controlled by Th1 cells is ADCC. This extracellular killing technique can be performed by neutrophils, macrophages, eosinophils, and NK cells, and requires the coexistence of specific IgG antibodies. What these cells have in common is the possession of CD16, the receptor for the Fc component of IgG. In one special case, IgE can mediate ADCC if the target is a parasitic helminth. In this case, the effector cells lack specificity for the altered cellular antigen, but the specificity of the idiotype of the antibody directs their release of perforin, lytic enzymes, and tumor necrosis factor (TNF).



▲ **Figure 7-2.4** ADCC

▼ **Table 7-2.0** Effector Mechanism Characteristics

Effector Cell	Identifying Markers	Antigen Recognition	MHC-restriction	Effector molecules
Macrophage	CD14+	Nonspecific	No	Intracellular digestion, TNF-α, NO, Oxygen radicals
Tc	CD3+, CD8+	Specific with TCR	Yes, class 1	Perforin, granzymes, LT, IFN-γ
NK cell	CD16+, CD56+	Lectins	No, MHC class 1 inhibits	Perforin, granzymes, LT, IFN-γ
ADCC	CD16+	By antibody	No	Perforin, granzymes, cytokines

Connection to Microbiology

Other than tumor cells, which tend to be genetically unstable and delete portions of their genome, therefore stopping expression of MHC class 1 molecules, many viruses have evolved evasive techniques to avoid Tc killing.

- Herpes viruses
- Hepatitis B (during hepatocellular carcinoma)
- Papillomaviruses
- Human immunodeficiency virus (HIV)

Connection to Microbiology

An example of a disease in which ADCC represents a crucial immune response is cytomegalovirus (CMV) infection. CMV is a herpes virus and therefore down-regulates expression of MHC class 1 on the cell surface. This makes CMV-infected cells refractory to Tc killing, so the mobilization of NK cells is expected. The problem with this, however, is that CMV additionally produces a fake MHC class 1 molecule, which is a close-enough replica to be able to fool the NK cell. Now the two major effectors of CMI are inactivated. What keeps the patient from dying of fulminating CMV infection is the ability of antibodies to recognize the fake molecules on the surface of the CMV-infected cells and target them for killing with ADCC.

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Immunologic Memory

1 Overview of Immunologic Memory

The activation of the immune response is antigen-driven. As long as antigen persists, cells continue to be activated, proliferate, and differentiate into effector cells. If the immune response is successful at destroying the invader, however, the system must return to its baseline homeostatic level so that energy is not wasted on a response that is no longer needed. It is during this return to a physiologic resting state that memory cells develop.

2 Activation-Induced Cell Death

The dampening of the specific humoral response when it is no longer needed is a natural consequence of the short life span of the plasma cell effector. Plasma cells live about two weeks, and if they are not replaced from the dividing pool of B lymphocytes, the antibody that they produce simply declines.

The process of restoring baseline homeostasis with cell-mediated responses is a more active one. This is because T cell cytokines can be harmful if they are produced in too great a quantity. Activation of T cells results in production of IL-2 and expression of two key cell surface proteins called *Fas* and *Fas ligand (FasL)*. When these two molecules become coexpressed and bind one another following repeated antigenic stimulation, a proteolytic cascade of caspases induces apoptosis. This process, *activation-induced cell death (AICD)*, plays a critical role in regulating the size of the T cell pool and removing T cells that might be responsive to self antigens.

USMLE® Key Concepts

For Step 1, you must be able to:

- List the mechanisms by which B and T memory lymphocytes are formed.
- Explain the recirculation patterns of memory cells.
- Describe how immune responses evolve over repeated stimulations.

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3 Characteristics of Memory Cells

The lymphocytes that survive after AICD, in the absence of continued antigenic stimulation, become long-lived memory cells. Memory B lymphocytes are believed to have about a 10-year lifespan, while memory T cells may last many decades.

▼ **Table 8-3.0** Naive, Effector, and Memory Lymphocytes

	Naive	Effector	Memory
T LYMPHOCYTES			
Recirculation	Secondary lymphoid organs	Areas of inflammation	Areas of inflammation
IL-2 receptor	Low	High	Low
Cell cycle	No	Yes	+/-
Effector functions	None	Cytokines and cytotoxicity	None
B LYMPHOCYTES			
Affinity	Low	Increasing	High
Isotype	IgM and IgD	IgG, IgA, or IgE	IgG, IgA, or IgE
Appearance	Small	Large	Small
Effector functions	Primary immune response	Antibody secretion	None

Clinical Application

The respiratory adenovirus vaccine administered to military recruits in boot camp is the only example of a live, non-attenuated viral vaccine on the market. It is delivered within an enteric capsule that releases the living virus within the intestinal mucosa, where it produces an asymptomatic intestinal infection. The memory cells generated in this way, however, recirculate to protect all of the mucosal surfaces of the body, and the military recruit is protected from the natural route of entry of adenoviruses across the respiratory mucosa.

4 Dissemination of Memory

During the memory phase, cells activated in secondary lymphoid organs at the time of the initial exposure migrate out to generalize the protection over the entire body. Memory cells tend to recirculate in a tissue-specific fashion, returning preferentially to the type of tissue in which they first encountered antigen. This process is mediated by differential expression of adhesion molecules on the surfaces of memory cells that appear to attract them specifically to particular types of tissues.

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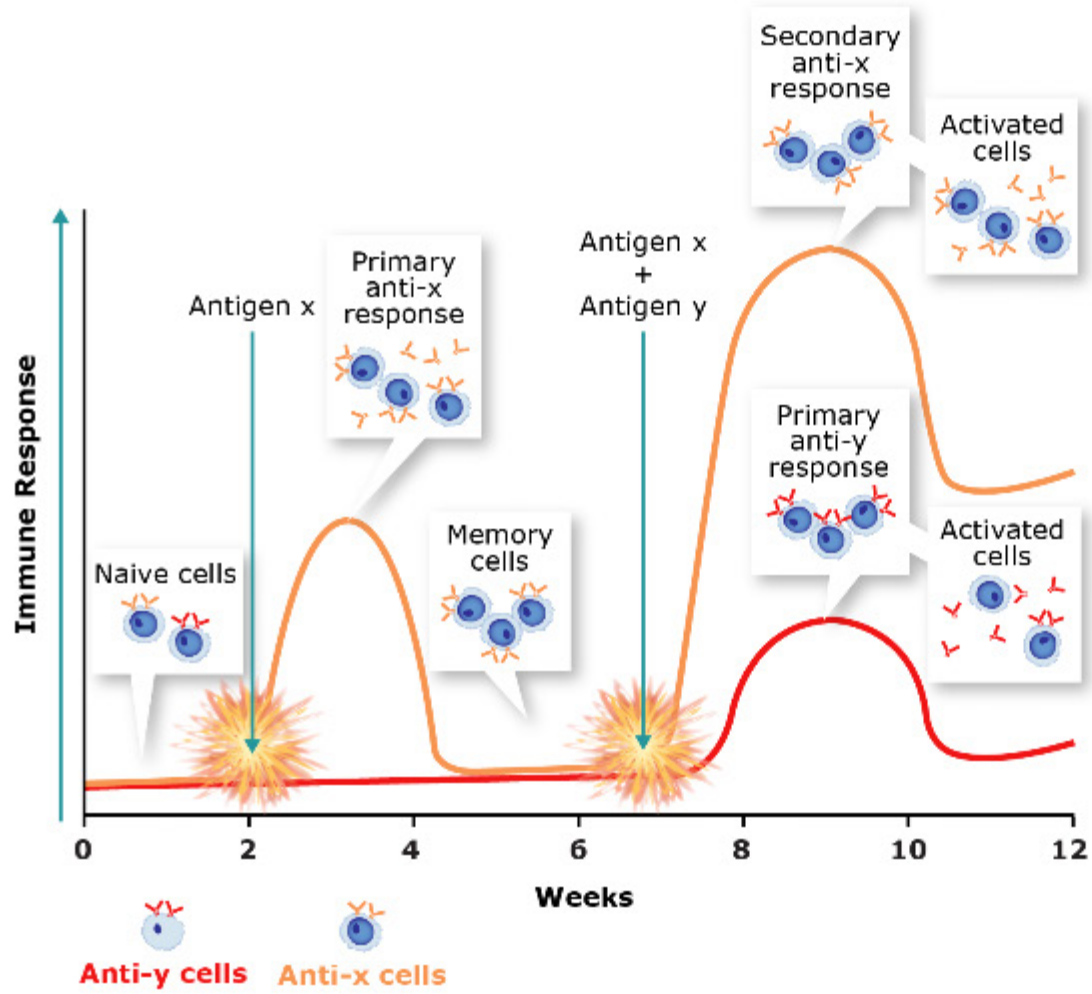
5 Comparison of Primary and Subsequent Immune Responses

When an antigen is introduced into the body for a second or subsequent time, each administration results in a response that is stronger, faster, and more refined. Because clonal expansion and memory cell production occurs with each administration, with each renewed exposure, the number of cells with appropriate specific antigen receptors becomes larger and larger.



▲ **Figure 8-5.0** Primary vs. Secondary Immune Responses

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Review Questions Chapters 6–8

1. A "knockout" mouse strain has been developed with a complete defect in a single gene product. The B and T lymphocyte counts in this strain are within normal parameters. Serum antibody measurements reveal high titers of IgM without significant presence of IgG, IgA, or IgE. Which of the following deficiencies best explains this mouse's condition?

A. B27
B. CD4
C. CD40L
D. IL-4
E. TNF-α

2. A biotech company has developed a new line of compounds prepared by proteolytic digestion of purified anti-nickel IgG antibodies. Compound A is prepared with papain. Compound B is prepared with pepsin. Which one of the two compounds is most useful as a positive control reagent for a nickel agglutination assay?

A. Compound A, because it contains the Fc fragment.
B. Compound B, because it contains the Fc fragment.
C. Compound B, because it contains the $F(Ab')^2$ fragment.
D. Compound B, because it contains Fab fragments.
E. Compound A, because it can activate complement needed for the agglutination assay.
F. Compound B, because it can still bind to the Fc receptors necessary for agglutination.

3. Marriage licenses in all 50 states of the United States require proof of rubella antibody titer. Which of the following descriptions fits the antibody isotype detected in this assay that would confer protection to any fetus?

A. A dimeric molecule found in secretions
B. A monomeric cell surface antigen receptor
C. An opsonin
D. A pentameric complement activator
E. Mast cell binding antibody

4. A child who has suffered repeated bacterial septicemias is found to have a genetic deficiency of complement component 6. When plasma from this patient is incubated with bacteria, which of the following outcomes is most likely?

	Production of Anaphylatoxins	Bacterial Lysis
A.	Decreased	Decreased
B.	Decreased	Normal
C.	Normal	Decreased
D.	Normal	Normal

5. A patient with hepatitis C hepatocellular carcinoma joins a trial protocol intended to stimulate production of CD8+ cells specific for his transformed cells. His MHC class 1 haplotype is determined to be A1/A7, B2/B3, and C2/C3. Which of the following molecules implanted into the membrane of cultured tissue fibroblasts enriched for expression of costimulatory molecules would serve to stimulate the most effective cytotoxic killing?

A. Whole hepatitis C virus
B. HCV core antigen plus HLA-A1
C. HLA-A1/7
D. HLA-B2/3
E. HLA-C2/3

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Chapters 6–8 Review Questions

6. Genetic testing of a family reveals that both parents are carriers of a mutation that produces a stop codon in the IFN-γ receptor. To which of the following pathogens would their homozygous child have most increased susceptibility?

A. *Bacillus anthracis*
B. *Chlamydia trachomatis*
C. Herpes simplex virus
D. *Listeria monocytogenes*
E. *Streptococcus pyogenes*

7. An investigator is conducting a study of immune responses to tumor cells in two groups of mice. Group 1 is inoculated with tumor cells transfected with the interleukin-2 gene. Group 2 is inoculated with non-transfected tumor cells. It is observed that the immune response in Group 1 is enhanced compared with the immune response in Group 2. This difference in immune response is best explained by enhanced proliferation of which of the following cell types in Group 1?

A. Dendritic cells
B. Macrophages
C. Neutrophils
D. Plasma cells
E. Tc lymphocytes

8. A strain of inbred mice is produced that spontaneously develops hypergammaglobulinemia, autoimmune disease, and excessive numbers of T cells in the blood. Which of the following is most likely to be the genetic defect?

A. Absence of complement
B. Absence of Fas
C. Absence of interferon-γ
D. Absence of perforin
E. Absence of tumor necrosis factor

9. A group of experimental rats are inoculated with tetanus toxoid (TT) three times, seven days apart, over a three-week period. The last injection of TT is mixed with anthrax toxoid (AT). Two days after the last injection, the rats are bled and their sera analyzed for the presence of antibodies to TT and AT. Which of the following antibodies would be present in elevated titers?

A. IgG against TT
B. IgG against TT and IgM against AT
C. IgG against TT and AT
D. IgG and IgM against TT
E. IgM against AT
F. IgM against TT and IgG against AT

10. In comparisons of the efficacy of the live attenuated intranasal influenza vaccine (FluMist) and the injectable killed virus vaccine, it has been shown that the intranasal vaccine provides much greater protection. Which of the following statements most likely explains this finding?

A. Killed viral vaccines produce humoral immunity.
B. Intramuscular inoculation produces anti-hemaglutinin antibodies.
C. Intramuscular inoculation produces IgM antibodies.
D. Intranasal inoculation produces mucosal memory cells.
E. Intranasal inoculation stimulates IL-2 secretion.

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Review Answers Chapters 6–8

1. The correct answer is C. CD40L is the costimulatory molecule on Th cells that promotes cytokine synthesis and causes isotype switching in B cells. If the mouse is capable of making only IgM, it has the correlate of the human hyper-IgM syndrome.

2. The correct answer is C. To produce agglutination with antibodies, two attached antigen-combining sites are necessary. This ability is retained when immunoglobulins are cleaved with pepsin because the two Fab regions remain attached at the hinge (a Fab'^2 fragment).

3. The correct answer is C. Production of IgG antibodies against rubella virus by a pregnant woman would confer protection to a fetus because IgG molecules are actively transported across the placenta. IgG is an opsonin, and also activates complement and mediates ADCC.

4. The correct answer is C. If a patient does not possess C6, the classical complement cascade runs as normal until that point and then stops. The order of the cascade is C1, C4, C2, C3, C5, C6, C7, C8, and C9. All of the anaphylatoxins (C3a, C4a, and C5a) occur before C6 in the cascade, so their function is normal. C6 is a component of the membrane attack complex that mediates bacterial lysis, so that process is decreased.

5. The correct answer is B. For a Tc to recognize and kill a virus-transformed hepatocyte, the peptides of the virus have to be presented in an MHC class 1-matched environment.

6. The correct answer is D. IFN-γ is the most important cytokine of the Th1 that activates macrophages. Therefore, this homozygous child will have difficulties with any facultative intracellular microbe. Listeria monocytogenes is the only facultative intracellular microbe on the list.

7. The correct answer is E. IL-2 is the main cytokine product of the Th1 cell that causes cloning of any cell capable of cell division. It is important in the amplification of the cells of CMI, both Tc and NK cells. The other cells involved in CMI are nondividing cells and therefore do not respond to IL-2 synthesis.

8. The correct answer is B. Failure of AICD is thought to be caused by defects in the normal T cell apoptotic pathway. Some of these defects are due to genetic absence of Fas or FasL. Others are due to defective caspase activation. The result of any of these defects is the continued proliferation of activated T cells and production of autoimmune disease.

9. The correct answer is B. Multiple inoculations of tetanus toxoid over three weeks promotes isotype switching in responding B lymphocytes. With only two days for the first exposure to anthrax toxoid, however, only IgM synthesis is measured.

10. The correct answer is D. Two factors make intranasal inoculation of this vaccine more effective. One is the route of administration, because the production of infection in the mucosa generates mucosal surface memory cells. The second issue is the value of a live attenuated virus rather than a killed one. Living virus vaccinations promote both CMI and HMI, whereas killed vaccines cause only antibody production.

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CHAPTER 9 Immunoprophylaxis and Immunotherapy

1 Forms of Immunologic Therapy

One of the areas in which immunology is used every day in medicine is in the application of vaccines and immunotherapy. Immunity can be induced actively or passively. Immunization is said to be *active* if the patient is mounting the immune response for himself, but of course this process requires at least 10 to 14 days to become protective. *Passive* immunotherapy refers to the delivery of a preformed immunological product (such as an antibody) to an individual. Both active and passive immunotherapies have *natural* and *artificial* forms.

▼ **Table 9-1.0** Types of Immunity

Type	Purpose	Examples
Natural active	Produce immune memory	Recovery from infection
Artificial active	Produce memory without danger of virulent disease	Vaccines: DTaP, hepatitis B, influenza, etc.
Natural passive	Protect the fetus and neonate	Transplacental IgG; breast milk and colostrum with IgA
Artificial passive	Post-exposure prophylaxis	Antivenins against snake and spider bites, pooled immunoglobulin against rabies, botulism, tetanus

USMLE® Key Concepts

For Step 1, you must be able to:

- Identify the immunological strategies behind the commonly used vaccines.
- Describe the molecular contents of the commonly used vaccines.
- Explain the risks and applications of passive immunotherapy.

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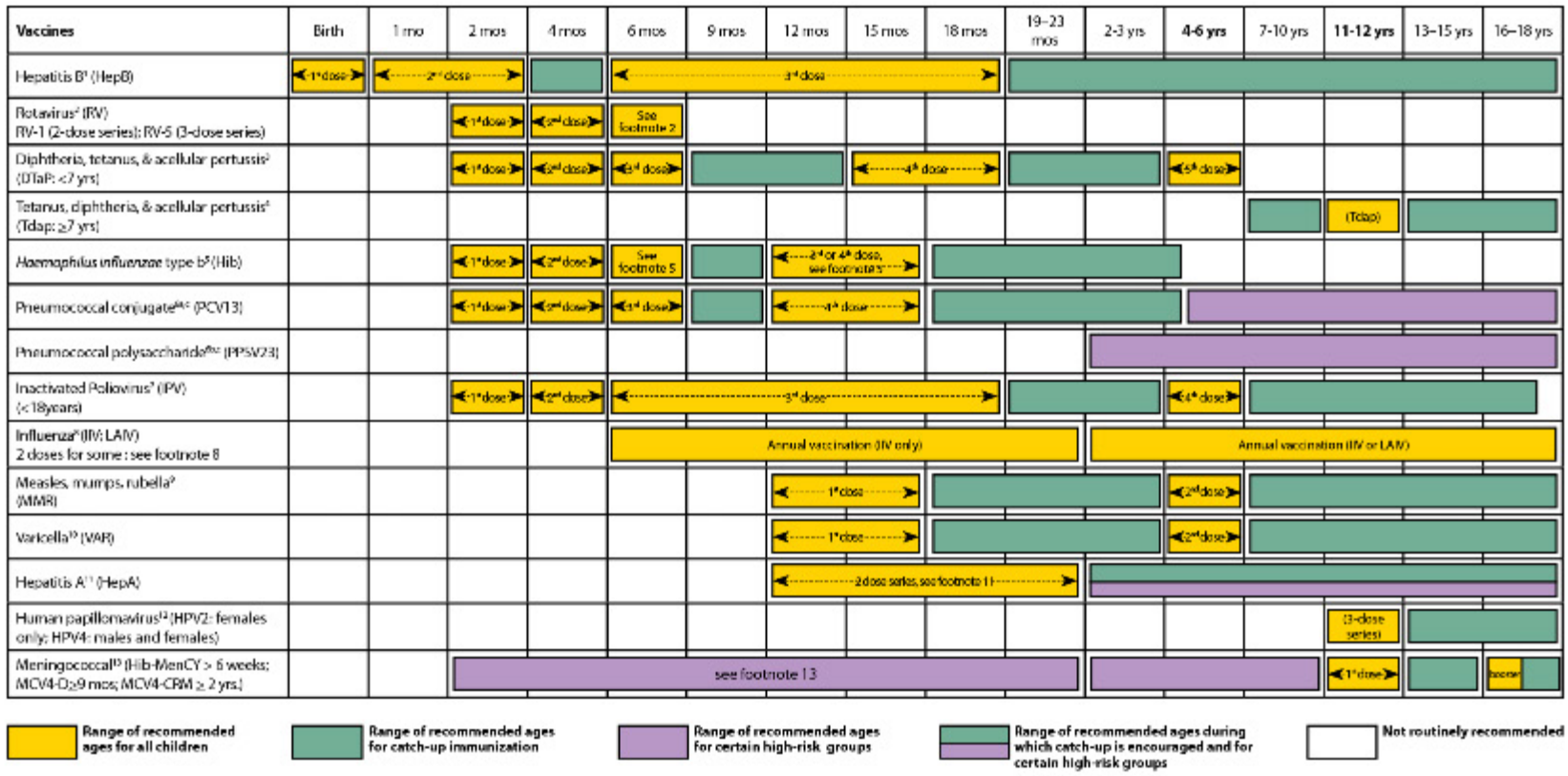
2 Active Immunization

Vaccination of children and adults has dramatically reduced morbidity and mortality due to infectious disease over the past 100 years. In the United States, vaccinations are recommended according to a schedule established by the Centers for Disease Control and Prevention.



For further guidance on the use of the vaccines mentioned, see: http://www.cdc.gov/vaccines/pubs/acip-list.htm .

▲ **Figure 9-2.0** CDC Schedule of Vaccinations

2.1 Bacterial Vaccines

Antibacterial vaccinations may be whole killed bacteria, live attenuated strains, toxoids, or single components. In the United States, only toxoid (inactivated toxin) or component (usually polysaccharide capsule) vaccines are in wide use.

▼ **Table 9-2.1** Bacterial Vaccines

Vaccine	Contents	Organism
DTaP	Toxoid Toxoid Toxoid + filamentous hemagglutinin	*Corynebacterium diphtheriae* *Clostridium tetani* *Bordetella pertussis*
Hib	Polyribitol phosphate capsule + protein	*Haemophilus influenzae* type b
PCV (pediatric)	13 capsular serotypes + protein	*Streptococcus pneumoniae*
PPV (adult)	23 capsular serotypes	*Streptococcus pneumoniae*
MCV4	4 capsular serotypes (Y, W-135, C, A) + protein	*Neisseria meningitidis*

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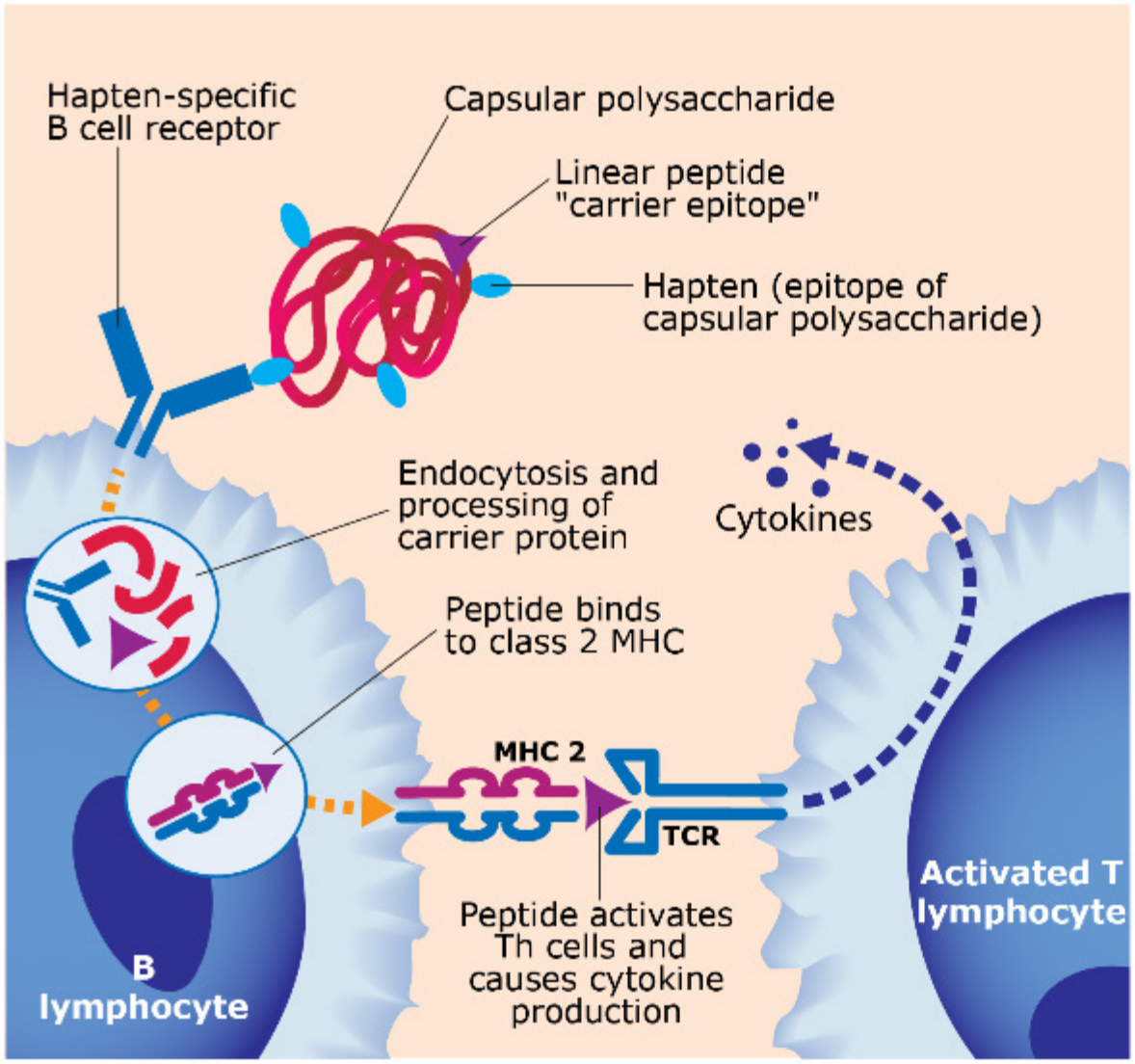
The immunological consequence of antibacterial vaccinations is the production of antibodies against the component of the inoculated organism. In the case of the DTaP, the patient produces *antitoxin antibodies* that block the binding of the native toxin to cells. In the case of the capsular vaccines (Hib, PCV, PPV, and MCV4), the result is *anti-capsular antibodies* that block the binding of the organism to the mucosal surfaces.

The necessity for the addition of protein to the pediatric capsular vaccines is a demonstration of the function of the *hapten-carrier effect*. In the immature immune response of a child under 5 years of age, it is necessary to optimize all conditions for artificial stimulation of the immune response. Although the goal of the Hib, PCV, and MCV4 vaccines is the production of antibodies against the capsular polysaccharide of the specific organism, if the vaccine contained no protein, there would be no Th2 sensitization, no isotype switching, no affinity maturation, and no memory. Therefore, these bacterial capsular polysaccharides are artificially conjugated to an unrelated protein (either the diphtheria toxoid or *Neisseria meningitidis* outer membrane proteins). The protein component of the vaccine is endocytosed by the polysaccharide-specific B lymphocyte, presented in the groove of MHC class 2 to a specific Th cell, and the result is cytokine production that fuels the differentiation of the capsule-specific B cell.



▲ **Figure 9-2.1** The Hapten-Carrier Effect in Conjugate Vaccines

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2.2 Viral Vaccines

There are three types of antiviral vaccines: attenuated live, killed, and recombinant DNA (component). The living viral vaccines are the most immunogenic, turning on the entire spectrum of the acquired immune response, but they have the risk of potential danger to the patient if the attenuated agent reverts to virulence. The killed viral and recombinant vaccines elicit humoral immunity only, but are safe, even in those who are immunocompromised. Vaccines made using recombinant DNA technology have intermediate immunogenicity and safety for all patient populations.

▼Table 9-2.2 Viral Vaccines

	Attenuated	Killed	Recombinant DNA
Potential for reversion	Yes	No	No
Safe in immunocompromised	No	Yes	Yes
Immunogenicity	High (CMI and Ab)	Lower (Ab only)	Middle (Ab to specific molecule)
Potential for contamination	Yes, live culture	No	No
Special storage	Yes	No	No
Examples	Measles, mumps, rubella, rotavirus, varicella zoster, adenovirus, Sabin polio	Rabies, influenza, Salk polio, hepatitis A	Hepatitis B, human papilloma virus

2.3 Adjuvants

Adjuvants are materials added to vaccines to increase immunogenicity nonspecifically. Aluminum salts or aluminum gels are the only vaccine adjuvants currently licensed for use in the United States. Adjuvants do not alter the nature of the immune response to vaccination; they simply increase the speed and amplitude of the response, perhaps by increasing nonspecific inflammation or by increasing the persistence of the immunogen at the injection site. Adjuvants are currently used in the vaccines for hepatitis A and B, DTaP, Hib, HPV, and adult pneumococcus. They are not used in live attenuated viral vaccines.

2.4 Vaccination and Pediatric Immune Development

One of the factors that must be considered in pediatric vaccine development is the concomitant maturation of the human immune response. In utero, of course, the fetus is passively protected by maternal IgG, which is actively transported across the placenta. In utero, from the second trimester onward, the fetus is capable of immunoglobulin synthesis, but in the sterile environment of the uterus, only IgM should be produced at baseline levels. As soon as the child is born and exposed to the less-than-sterile environment of the outside world, the child begins to isotype switch, making IgG first as dictated by the sequence of the germline DNA.

- Vaccines contraindicated during pregnancy—MMR (the rubella component).
- Vaccines contraindicated in patients with egg allergy—influenza, yellow fever.

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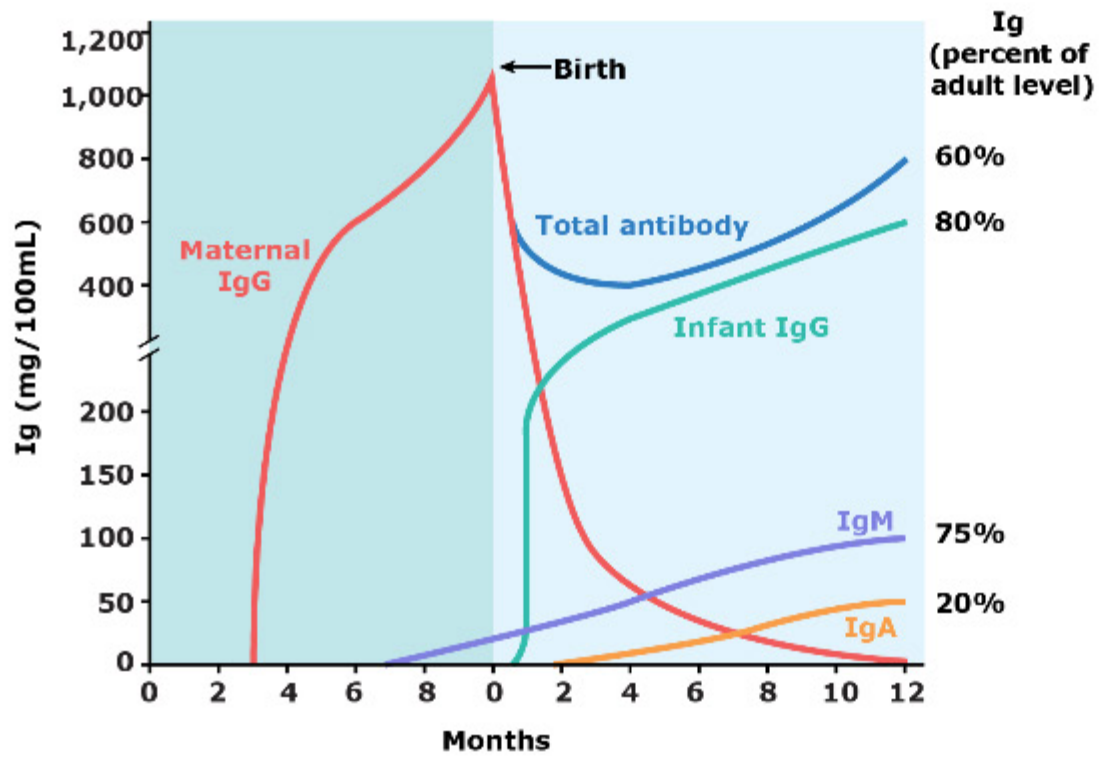
At parturition, the influx of maternal IgG is stopped, and that antibody concentration declines in the child following a normal protein catabolic curve. The child's immune response now operates in a race against time, trying to develop his own immune response to substitute for the waning passive immunity from the mother. Because the development of normal levels of IgA synthesis does not occur until well into the second year of life, IgA transferred in colostrum and breast milk plays a critical role in protection from mucosal pathogens in this period.



▲ **Figure 9-2.4** Immunoglobulins in Fetus and Newborn Infant

Clinical Application

- Administration of live viral vaccines in the first six months of life is unproductive due to the presence of maternal antibodies.
- Immunologic deficiency diseases usually do not present until maternal antibodies are gone.
- Elevated IgG cannot be used to diagnose in utero infections; the only fetal antibody that can be proven to come from the child is IgM.

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3 Passive Immunotherapy

Passive immunotherapy is used for post-exposure prophylaxis in cases when either the patient is incapable of making the response or there is not enough time for the response to be made before the disease effects could become dangerous.

The risks of passive immunotherapy are actually greater than the risks of vaccination. Because antibodies are proteins, and because the human species is extremely out-bred, the antibodies of one individual can be recognized by a recipient, and an immune response against the donated serum can result. These can be dangerous if immune complexes form, and *type III hypersensitivities* can result. If the anti-antibody response happens to be of IgE isotype, fatal anaphylactic reactions (type I hypersensitivity) can result. In these cases, the recipient of the passive immunotherapy is recognizing and responding to minor genetic polymorphisms that exist in the constant domains of the immunoglobulin molecule called *allotypes*.

Patients with selective *IgA deficiency* are particularly at risk for the development of anaphylactic responses against infused serum. In the absence of an ability to make IgA, these patients are extremely prone to producing IgE, and often the diagnosis of their immunodeficiency is only made following a serious hypersensitivity reaction to a simple, matched blood transfusion.

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1 Primary Immunodeficiencies

Primary immunodeficiencies are flaws in the functioning of the immune system that result from genetic defects in the expression of one or more of the working parts. Many of these are discussed in the Clinical Cases presented in this book. Here, the focus is on differential diagnosis and comparative pathogenesis.

1.1 Phagocyte Defects

Diseases are ranked in the table below in order of their likelihood of appearing in Step 1 questions. Phagocytes are critical in the protection from *extracellular* microbes, and some are critical antigen-presenting cells.

▼Table 10-1.1 Phagocyte Defects

Disease	Molecular Basis	Symptoms and Signs
Chronic granulomatous disease (CGD)	Deficiency of *NADPH oxidase*, failure to generate oxygen radicals for intracellular killing	Repeated infections with *catalase-positive* microbes NBT negative
Leukocyte adhesion deficiency	Absence of *CD18* from β2 integrins	Chronic extracellular microbial infections, failure to form abscesses and pus, omphalitis
Chediak-Higashi syndrome	Granule structural defect *(giant granules)* in NK cells and phagocytes	Chemotactic and degranulation defects, absent NK activity, partial *oculocutaneous albinism*
G6PD (glucose-6-phosphate dehydrogenase) deficiency	Loss of essential enzyme of the hexose monophosphate shunt	As in CGD plus anemia
Myeloperoxidase deficiency	Deficiency of granule enzyme	Usually clinically silent
Job syndrome	No IFN-γ from Th1 cells, phagocytes do not respond to chemotactic stimuli	Cold abscesses, retained primary teeth, eczema, increased IgE

USMLE® Key Concepts

For Step 1, you must be able to:

- Diagnose and explain the molecular basis of pathogenesis for the most important primary and acquired immunodeficiency diseases.
- Describe the molecular basis of HIV/AIDS pathogenesis on the immune response.

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1.2 Humoral Immune Defects

Diseases are ranked in the table below in order of their likelihood to appear in Step 1. The humoral immune response is critical in the defense against extracellular microbes.

▼**Table 10-1.2** Humoral Immune Defects

Disease	Molecular Basis	Symptoms and Signs	Therapy
Bruton X-linked agammaglobulinemia	Lack of *tyrosine kinase* involved in B cell maturation	B cell development stopped at pre-B level, no circulating B cells, no immunoglobulin	Monthly immunoglobulin replacement, antibiotics for infections
Hyper IgM syndrome	Deficiency of *CD40L* on Th cells	Elevated IgM titers, no other isotypes, normal B and T cell numbers	Antibiotics and immunoglobulins
Selective IgA deficiency	Decreased expression of C-α in the germline B cell (most common)	Repeated infections of mucosal surfaces, increased *atopic allergy*	Antibiotics, no immunoglobulins
Common variable immunodeficiency	Mutation in transmembrane activator and cyclophilin ligand interactor (TACI) that mediates isotype switching	Onsets late teens, B cells present, immunoglobulin levels decrease over time, increased autoimmunity	Antibiotics

1.3 Complement Deficiencies

This form of immunodeficiency is caused by the absence or impaired functioning of one of the complement system proteins. Again, the diseases in the table below are ranked according to their likelihood of appearing in Step 1 questions.

▼**Table 10-1.3** Complement Deficiencies

Cascade Involved	Component Missing	Signs and Symptoms	Therapy
Classical	C1q, C1r, C1s, C4, C2	Increased immune complex disease, infections, extracellular microbes	Fresh-frozen plasma to replace components
All pathways	C3	Immune complex disease, repeated extracellular microbe infections	As above
	C5–C9	Repeated neisserial bacteremias	As above
Deficiencies of Complement Regulation			
Classical	C1-INH (hereditary angioedema)	Overuse of C1, C4, C2, edema at mucosal surfaces	Infusion of C1 esterase inhibitor, androgen therapy
All pathways	Absence of DAF and MIRL on stem cell precursors; acquired; paroxysmal nocturnal hemoglobinuria	Hemoglobinuria, occasional, in mornings, thrombocytopenia, leukocytopenia	Stem cell transplantation, eculizumab (blocks formation of membrane attack complex)

1.4 T Lymphocyte Defects

Because T cells play a central role in activation, differentiation, amplification, and modulation of virtually all immune responses in the body, defects in their function often have global implications on health. Patients with these defects tend to have problems first with microbes that are handled with CMI. Fungi represent other problem microorganisms for those with T lymphocyte defects.

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▼**Table 10-1.4A** T Lymphocyte Defects

Disease	Defect	Symptoms and Signs
DiGeorge syndrome (velo-cardio-facial syndrome)	Failure of formation of 3rd and 4th pharyngeal pouches, 22q11.2 deletion	Thymic aplasia, abnormal facies, hypoparathyroidism, cardiac malformations, decreased T cell numbers, absence of T cell responses
MHC class 1 deficiency	Failure of TAP molecules to transport peptides to endoplasmic reticulum	Deficiency of CD8+ T cells, normal Th cells; elevated NK activity; normal type IV hypersensitivity and antibody production

Dr. P. Marazzi/Science Source

▲**Figure 10–1.4A** DiGeorge Syndrome

▼**Table 10-1.4B** Combined Partial B and T Cell Deficiencies

Disease	Defect	Symptoms and Signs
Wiskott-Aldrich syndrome	X-linked defect in *WASp* causes defective cytoskeletal signaling	Eczema, thrombocytopenia and variable immunodeficiency (usually IgM)
Ataxia telangiectasia	*ATM protein kinase* defect causes inability to repair dsDNA breaks	Spinocerebellar degeneration, telangiectasias, diminished IgG, IgA, and IgE synthesis

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▲**Figure 10–1.4B** Wiskott-Aldrich Syndrome

1.5 Severe Combined Immunodeficiencies (SCIDs)

When both B and T lymphocytes are absent or nonfunctional, severe combined immunodeficiencies (SCIDs) result. Without bone marrow transplantation, most of these conditions are incompatible with long-term survival.

▼**Table 10-1.5** Severe Combined Immunodeficiencies (SCIDs)

Disease	Defect	Symptoms and Signs
Bare lymphocyte syndrome	Failure of MHC class 2 expression, defects in transcription factors	Deficient CD4+ cells, no graft vs. host disease, hypogammaglobulinemia
IL2R SCID	X-linked defect in common γ chain of IL-2 receptor (also in IL-4, -7, -9, -15)	Lymphocytopenia, chronic diarrhea, lesions of mucosa, no response to mitogens
Adenosine deaminase deficiency	Buildup of toxic product of purine metabolism in lymphocyte precursors	As above
RAG gene SCID	*RAG1* or *RAG2* gene nonsense mutations	Lymphocytopenia

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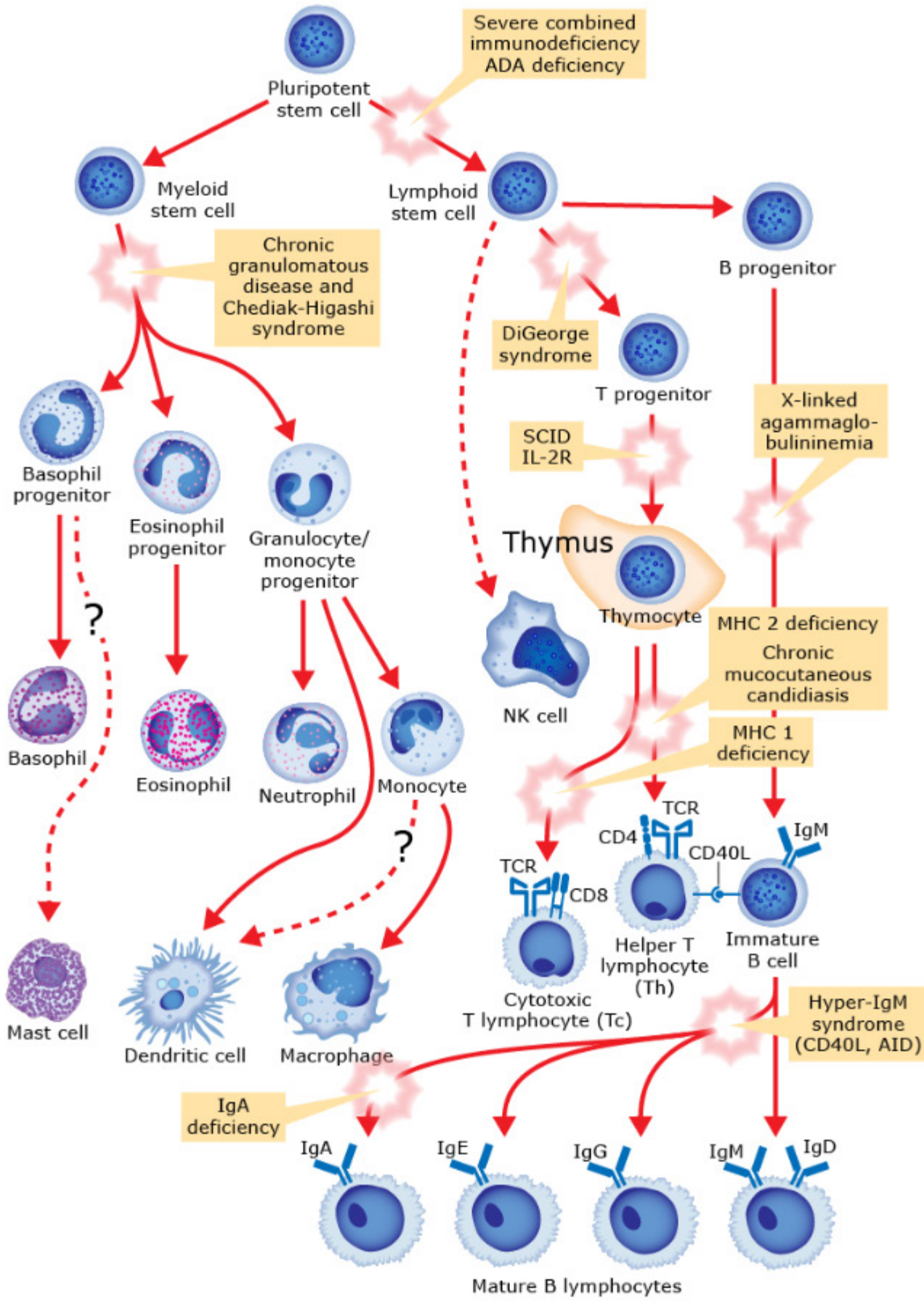

▲ **Figure 10-1.5** Immunodeficiency Diseases and Developmental Blocks

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2 Acquired Immunodeficiencies: HIV/AIDS

Acquired (or secondary) immunodeficiencies are not caused by inherited defects within the immune system, but rather by immunosuppressive agents or diseases. While many forms of cancer and some chronic infections can cause immunosuppression, HIV is the one virus most closely associated with this condition.

2.1 Characteristics of HIV

Human immunodeficiency virus (HIV) is a lentivirus belonging to the retrovirus family. It attaches to Th cells and antigen-presenting cells using the CD4 receptor and chemokine receptors. Early in infection, the virus disseminates throughout the body by infecting macrophages using the *CCR5 chemokine receptor*, and in this phase, the virus is said to be macrophage tropic *(M-tropic)*. Later in infection, the virus uses the *CXCR4 chemokine* receptor found on Th cells and becomes T-tropic.

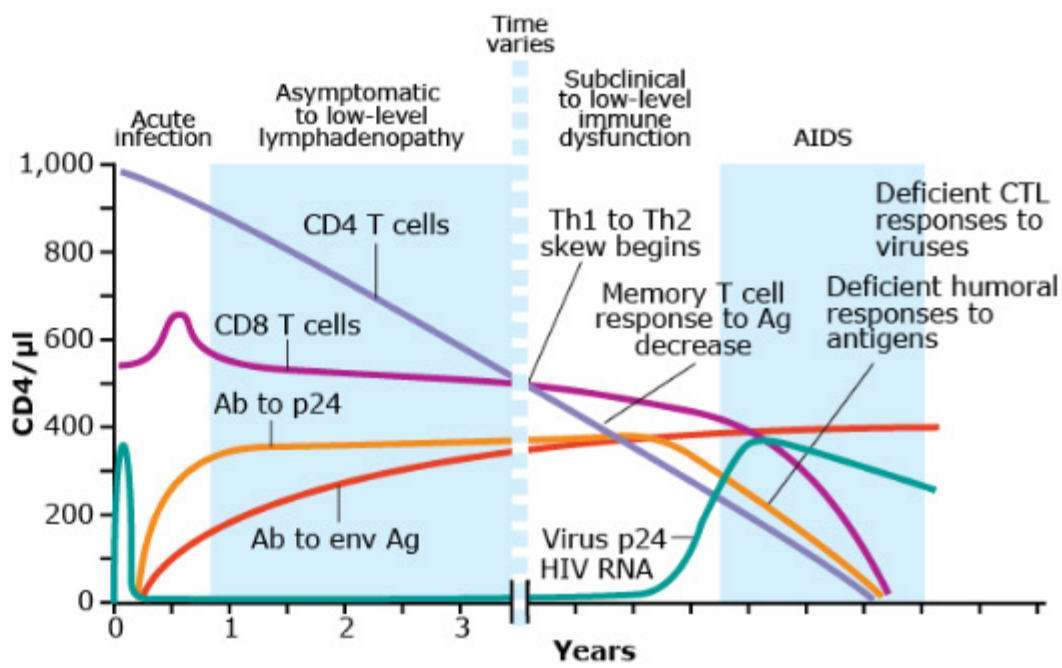
2.2 Course of Infection

When the patient is first exposed to HIV, the virus spreads throughout the body and establishes a lifelong reservoir in long-lived tissue macrophages. The acute infection is asymptomatic or at most associated with influenza-like symptoms. The first antibody produced is the antibody against the *capsid protein* of the virus *(p24)*, and antibodies to envelope antigens (gp41 and gp120) are produced shortly thereafter. The presence of p24 antibodies keeps the virus out of the circulation for most of the course of infection. As the virus kills CD4 cells, the normal CD4 cell count falls from approximately 1000/mm³.

- **400 CD4 cells/mm³:** At this cell count the patient begins to suffer signs of *immunological dysfunction* as T cell responses decline: weight loss, generalized lymphadenopathy, fatigue, and night sweats. The production of antibodies to p24 begins to fall at this point, since these are IgG isotype antibodies that are not produced in the absence of T cell help. Antibodies against envelope antigens remain elevated until death, since these are IgM antibodies synthesized anew in response to the constant mutational change of these viral molecules.
- **200 CD4 cells/mm³:** When the CD4 count falls to this point and lower, *acquired immunodeficiency syndrome (AIDS)* is diagnosed by the concomitant infection with an AIDS-defining opportunistic microbe. At this point, the immune response no longer has sufficient Th cells to mediate any immune response other than IgM synthesis and innate mechanisms.

Clinical Application

Patients who are homozygous for mutations to the CCR5 chemokine receptor cannot be infected with HIV. Patients who are heterozygous for this mutation experience a slower course of infection. The new anti-retroviral drug, maraviroc, is a CCR5 receptor antagonist.



▲ **Figure 10-2.2A** Course of Untreated HIV

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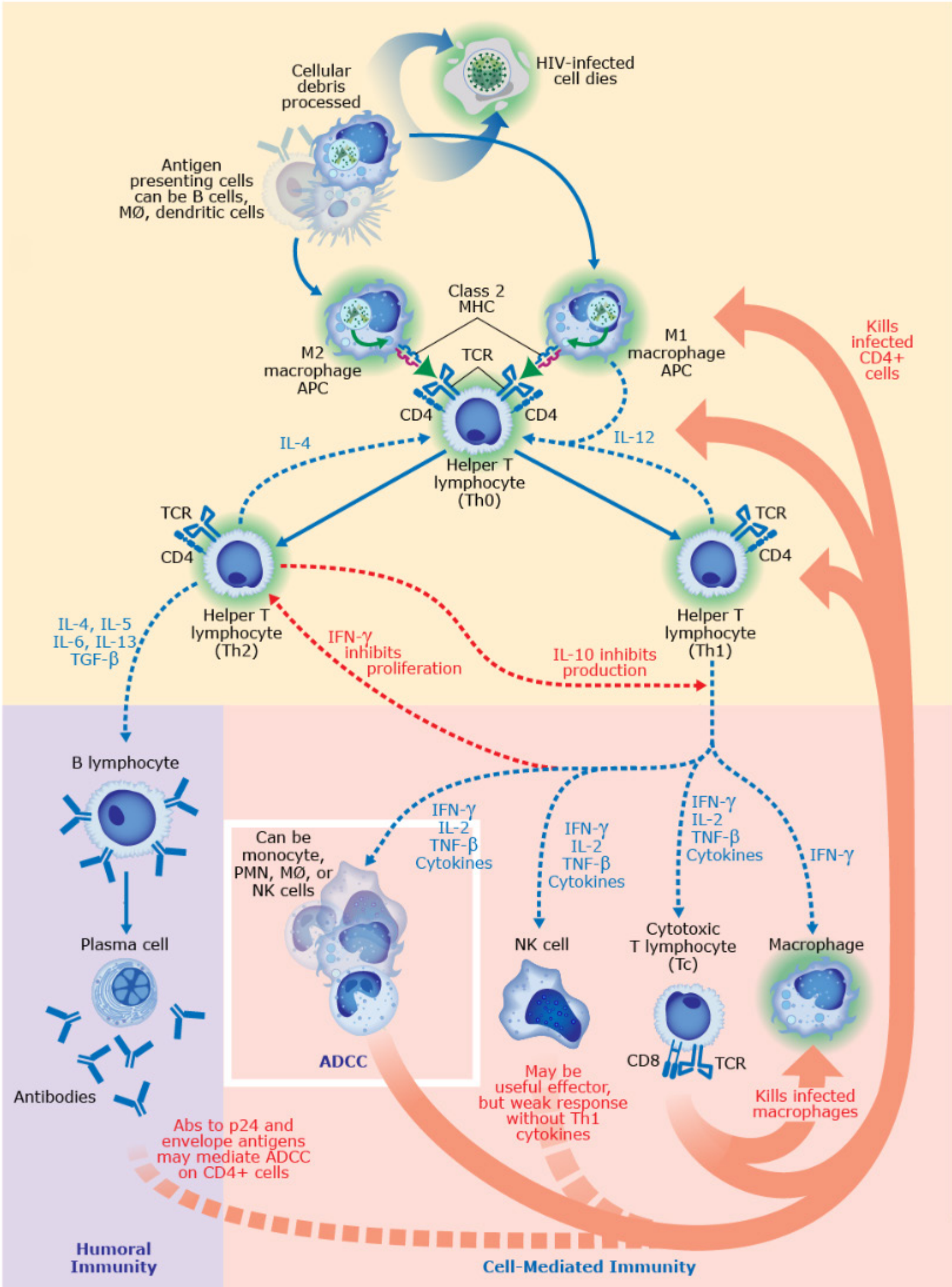

▲ **Figure 10-2.2B** HIV Effects on Immune System

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Chapters 9–10 Review Questions

1. A patient being studied for an unusual immunologic disorder is found to lack class 1 MHC molecules, and homogenized lymphocyte precipitates are found to lack TAP1 molecules. Which of the following vaccines would most likely be ineffective in this patient?

A. Diphtheria, tetanus, acellular pertussis (DTaP)
B. Human Papillomavirus
C. Measles, mumps, rubella (MMR)
D. *Neisseria meningitidis*
E. *Streptococcus pneumoniae*

2. A child is taken to the pediatrician because of his mother's suspicion of food allergies. Skin testing is positive for hypersensitivity to egg albumin. Which of the following vaccinations would be contraindicated in this child?

A. *Haemophilus influenzae*
B. Hepatitis B
C. Influenza
D. Measles, mumps, rubella
E. Rotavirus

3. Prior to 1990, pediatric vaccines against *Haemophilus influenzae* type B contained capsular material from the organism plus an adjuvant. What immune response is expected from this inoculation?

A. Th lymphocyte activation
B. Cytotoxic T lymphocyte stimulation
C. IgM production
D. Immunologic memory induction
E. Isotype switching

4. If patients receiving the Salk polio vaccine are compared with those receiving the Sabin vaccine, which of the following statements is most likely to be true?

A. Only recipients of the Sabin vaccine will develop Th1-mediated immunity.
B. Only recipients of the Sabin vaccine will develop Th2-mediated immunity.
C. Only recipients of the Salk vaccine will develop specific IgA antibodies.
D. Only recipients of the Salk vaccine will develop Th1-mediated immunity.
E. Only recipients of the Salk vaccine will develop protection at the gastrointestinal mucosa.

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Review Questions Chapters 9–10

5. A 35-year-old man suffers a lacerated spleen as a result of an automobile accident. Which of the following vaccines should be administered before he is released from the hospital following splenectomy?

A. Hepatitis B
B. Influenza
C. MMR (measles, mumps, rubella)
D. Pneumococcal (23-valent)
E. Td (tetanus-diphtheria)

6. A female neonate with low birth weight is evaluated because of dysmorphic facial features and generalized cyanosis. Shortly after delivery, she developed seizures resulting from severe hypocalcemia. What additional findings are most likely in this individual?

A. Decreased alpha-fetoprotein
B. Decreased IgA levels
C. Diminished numbers of CD3+ cells
D. Elevated IgM levels
E. Prominent telangiectasias around the eyes

7. A 6-month-old boy is seen by his pediatrician for epistaxis. The patient has a history of multiple bacterial and viral respiratory tract infections and eczema. Serum IgM is decreased, IgG is normal, and IgA and IgE are increased. The mean diameter of platelets is decreased. Which of the following is the most likely defect?

A. Absence of a cytoskeletal signaling protein
B. Absence of interleukin-11
C. Absence of NK cells
D. Failure of dsDNA repair
E. Thymic hypoplasia

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Chapters 9–10 Review Questions

8. A man who is seropositive for HIV has a CD4+ T lymphocyte count of 495. Which of the following is likely to be most decreased in this patient?

A. Antibody-dependent opsonization
B. Interleukin-2
C. Mast cell degranulation
D. NADPH oxidase
E. Tumor necrosis factor

9. A 43-year-old HIV-positive man goes to his physician complaining of a two-month history of cough that has recently brought blood up into his mouth. His CD4+ T lymphocyte count is 435/mm^3. A chest radiograph shows opacities in the right upper lobe. Which of the following immunologic measurements is most likely to have direct correlation to the progression of his disease?

A. IgM synthesis
B. Intracellular microbial killing
C. NK cell activity
D. Type I hypersensitivity
E. Type IV hypersensitivity

10. A 3-year-old boy is seen by a pediatric specialist after developing cellulitis for the third time in four months. The doctor notes that the boy has pale hair, blue eyes, and patchy hypopigmentation of the skin. Attempts at funduscopic examination reveal moderate photophobia. Oral ulcers also are noted. Blood testing reveals neutropenia and hypergammaglobulinemia. Blood smear will most likely reveal which of the following?

A. Lymphocytosis
B. Elevated reticulocytes
C. Mononuclear cells with "owl's eye" nuclei
D. Granulocytes with giant granules
E. Irregularly shaped lymphocytes

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Review Answers Chapters 9–10

1. The correct answer is C. To elicit a cell-mediated response to a live-attenuated viral vaccine, the patient must express MHC class 1 molecules on the surface of his cells. All of the other vaccines listed evoke an antibody response that would be possible in the absence of MHC class 1 expression.

2. The correct answer is C. Influenza and yellow fever vaccines are prepared in eggs, and therefore may have allergenic doses of egg albumin in them. The viruses in the measles, mumps, and rubella vaccine also are grown in hen's eggs, but the amount of egg albumin is so minimal that this vaccine has been removed from the contraindication list.

3. The correct answer is C. Capsular polysaccharides elicit only IgM antibodies unless they are conjugated covalently to protein. The use of an adjuvant in this setting only makes the response happen faster.

4. The correct answer is A. The Salk polio vaccine is a killed vaccine that is injected intramuscularly. Thus, it causes the production of humoral but not cell-mediated immunity. The Sabin (live, oral) polio vaccine elicits immunity in the mucosal-associated lymphoid tissues, and stimulates the production of both cell-mediated and humoral immunity against the virus.

5. The correct answer is D. Splenectomized patients are at special risk for infections with encapsulated organisms. Because the spleen is the largest antibody-producing organ in the body, it filters pathogens from the blood, and the vascular sinusoids promote the actions of opsonization and phagocytosis. Of the vaccines on the list, only the pneumococcal vaccine protects against an encapsulated organism.

6. The correct answer is C. This infant has DiGeorge syndrome or velocardiofacial syndrome. It is a deletion of chromosome 22q11.2 that results in facial dysmorphia (low-set ears, hypertelorism, micrognathia, failure of formation of the parathyroids and thymus, and cardiac defects such as truncus arteriosus.

7. The correct answer is A. This child has Wiskott-Aldrich syndrome, which results from a defective cytoskeletal signaling protein. The disease is identified as a triad of symptoms: eczema, thrombocytopenia, and immunodeficiency.

8. The correct answer is B. The parameter on this list that has the clearest correlation to the CD4 cell count is the production of IL-2. The only source of IL-2 in the immune system is from Th cells, thus, as their numbers decline, so does the body's ability to amplify the immune response by cloning.

9. The correct answer is E. This HIV-positive patient has developed reactivational tuberculosis due to his declining CD4 T cell count. Of the parameters on the list, the one that has the highest correlation with the CD4 count decline is the test that has the strongest requirement for Th1 cells, type IV hypersensitivity.

10. The correct answer is D. This patient has Chediak-Higashi syndrome, a defect of granule activity in NK cells and phagocytes.

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1 Overview of Hypersensitivity and Autoimmunity

Hypersensitivity diseases occur when there is too much immune response, and the resulting immune products damage host tissues. Hypersensitivities include responses to foreign antigens as well as failures of self-tolerance, which are referred to as *autoimmune diseases*. Excesses of the immune response are classified into four general types based on the molecular basis of pathogenesis.

▼Table 11-1.0 Types of Hypersensitivity

Type	Pathogenesis	Effectors of Damage
I (immediate)	IgE	Mast cells and basophils
II (antibody-mediated)	IgM and IgG against cell or tissue antigens	Opsonization and phagocytosis, complement-mediated lysis and inflammation
III (immune complex)	Circulating immune complexes	Opsonization and phagocytosis, complement-mediated lysis and inflammation
IV (delayed-type)	Th1 cells and cytokines	Macrophage activation and granuloma formation Tc-killing, cytokine-driven inflammation

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the molecular basis of pathogenesis for each of the four forms of hypersensitivity disease.
- Identify the molecule, cell, or tissue targeted by the major autoimmune diseases.

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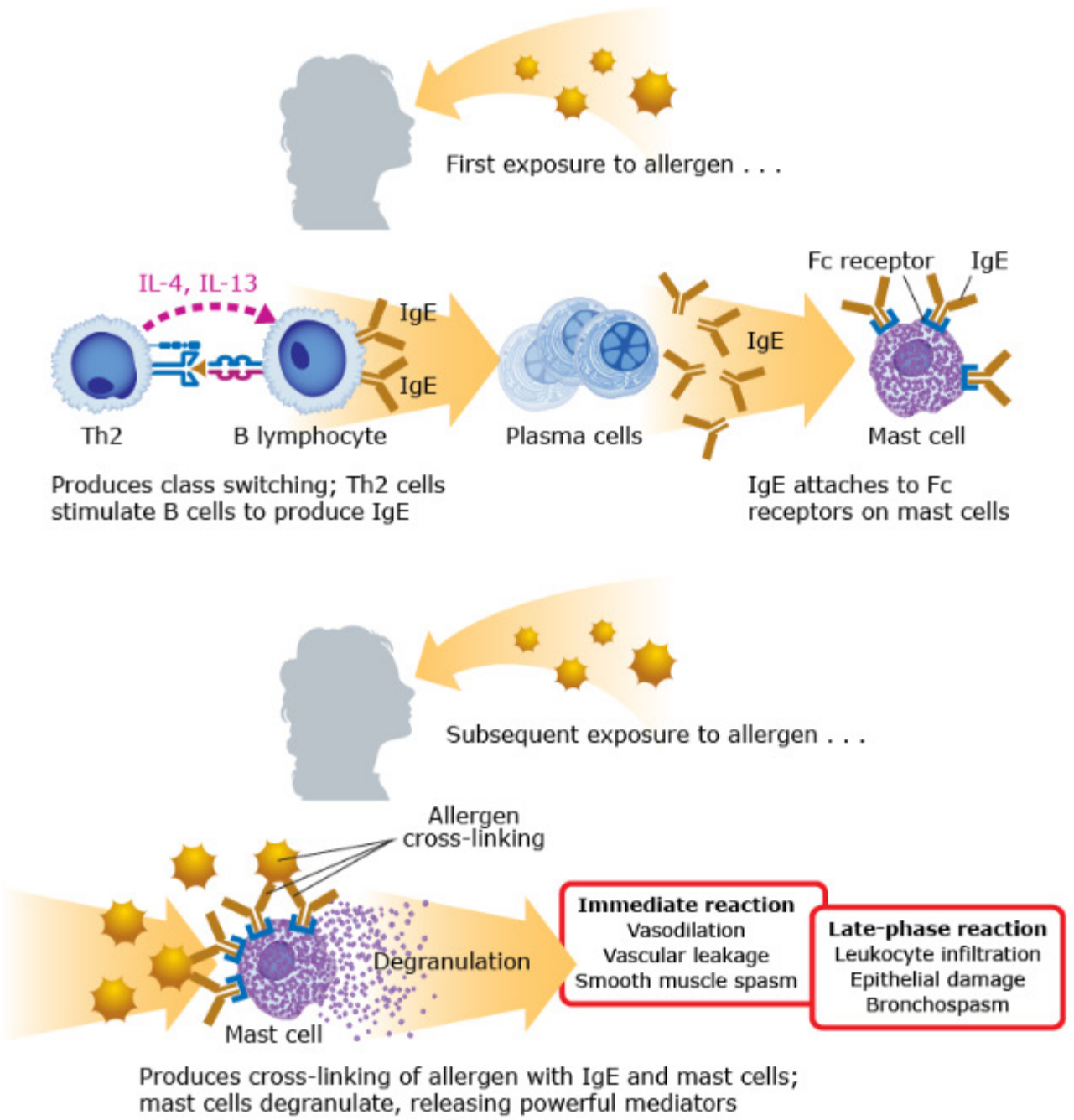
2 Type I Hypersensitivity

Type I hypersensitivity is the only form of hypersensitivity mediated by *immunoglobulin E*, *mast cells*, and *basophils*. It represents the body's natural response against helminth parasites that are too large to be killed by other immune responses.

2.1 Mechanism

When the body mounts a type I hypersensitivity against harmless environmental substances such as dust or animal dander or pollen, the result is *atopic allergy*. It is also known as *immediate hypersensitivity*, since the manifestations of tissue damage happen immediately on re-exposure to an allergen after sensitization.



▲ **Figure 11-2.1** Development of Type I Hypersensitivity

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2.2 Mediators

After their membrane-bound IgE molecules become cross-linked by repeated exposures to allergens, the degranulation of mast cells and basophils results in the release of a variety of pharmacologically active mediators. Release of these granular contents causes immediate smooth muscle contraction and increased vascular permeability. Four to six hours later, the late-phase reaction adds additional smooth muscle contraction, inflammation, and vascular permeability due to the production of mediators from the arachidonic acid cascade.

▼**Table 11-2.2A** Type I Hypersensitivity Mediators

Granule Contents	Result
Histamine	Smooth muscle contraction, increased vascular permeability
Heparin	Anticoagulant
Eosinophil chemotactic factor A	Chemotactic
Late-Phase Mediators	
Prostaglandin D2, E2, F2α	Smooth muscle contraction and vascular permeability
Leukotrienes C4, D4, E4	Smooth muscle contraction and vascular permeability
Leukotriene B4	Chemotactic for neutrophils

▼**Table 11-2.2B** Type I Hypersensitivities

Disease	Allergen	Symptoms and Signs
Allergic rhinitis (hay fever)	Pollen, dust, mites, animal dander	Edema, irritation, and mucus in nasal mucosa
Systemic anaphylaxis	Insect stings, drug reactions	Bronchial and tracheal constriction, vasodilation, death
Wheal and flare	Skin testing for allergies	Skin edema, vasodilation
Asthma	Inhaled materials	Bronchial and tracheal constriction, edema, mucus, inflammation
Food allergies	Eggs, milk, nuts, grains	Hives and gastrointestinal edema

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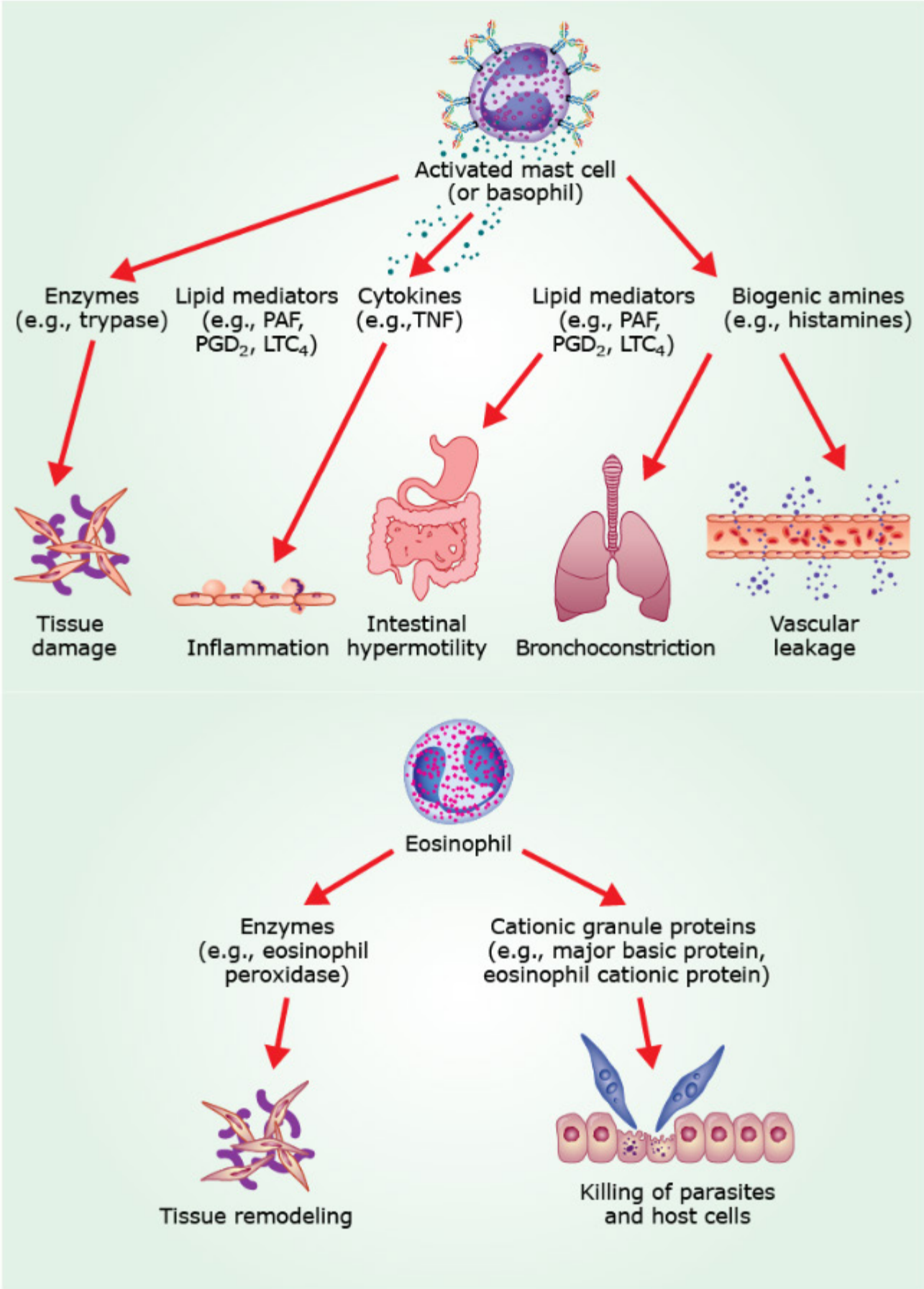

▲ **Figure 11-2.2** Type I Hypersensitivity Mediators

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3 Type II Hypersensitivity

Type II hypersensitivities are all autoimmune and directed specifically against a cell or tissue of the patient.

3.1 Mechanism

Type II hypersensitivities cause tissue damage by three main mechanisms:

- Opsonization or complement activation.
- Recruitment of inflammatory cells like PMNs and macrophages.
- Antibodies may bind to normal cellular receptors and cause interference with normal cellular function without cell lysis.

3.2 Cytotoxic and Non-Cytotoxic Type II Hypersensitivities

Cytotoxic hypersensitivities are those in which cell death is the result of the autoantibody binding and activating complement or encouraging phagocytosis. In the non-cytotoxic hypersensitivities, the functioning of the cell is altered, but cell death is not the immediate result.

▼ **Table 11-3.2A** Cytotoxic Type II Hypersensitivities

Disease	Antigen	Pathogenesis	Symptoms and Signs
Autoimmune hemolytic anemia, hemolytic disease of the newborn	Rh or other RBC membrane proteins	Opsonization, complement-mediated lysis	Hemolysis, anemia
Rheumatic fever	*Streptococcus pyogenes:* cell-wall antigen cross-reacts with myocardium	Inflammation, opsonization	Myocarditis, arthritis
Goodpasture syndrome	Type IV collagen in basement membranes	Complement and opsonization	Linear deposits of antibody in kidney and lung, nephritis
Transfusion reaction	ABO glycoproteins	IgM isohemagglutinins made in response to normal flora cross-react with alloantigens, activate complement, and cause opsonization	Hemolysis
Autoimmune thrombocytopenic purpura	Platelet membrane proteins	Opsonization and complement-mediated destruction of platelets	Bleeding dyscrasia

▲ **Figure 11-3.2A** Hemolytic Disease of the Newborn

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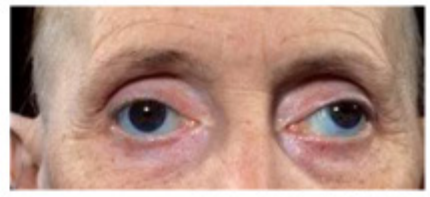
▼ **Table 11-3.2B** Non-Cytotoxic Type II Hypersensitivities

Disease	Antigen	Pathogenesis	Symptoms and Signs
Graves disease	Thyroid-stimulating hormone receptor	Antibody-mediated stimulation of secretion of T3, T4	Hyperthyroidism followed by hypothyroidism; biopsy negative for cell injury
Myasthenia gravis	Acetylcholine receptor	Antibody blocks acetylcholine binding, down-regulates receptors	Muscle weakness, paralysis
Type II (non-insulin-dependent) diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia

Dr. P. Marazzi/Science Source

▲ **Figure 11-3.2B** Graves Disease



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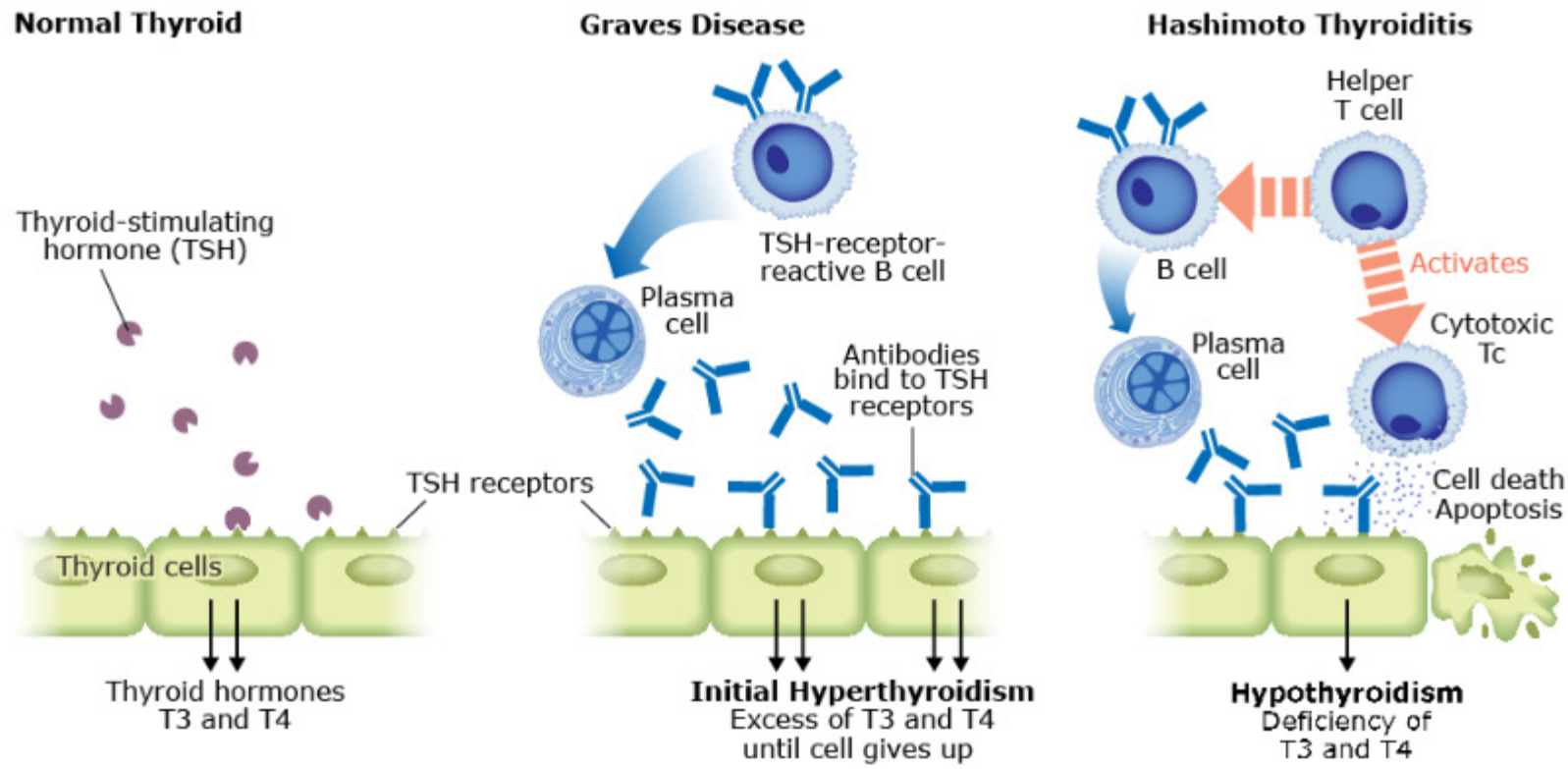
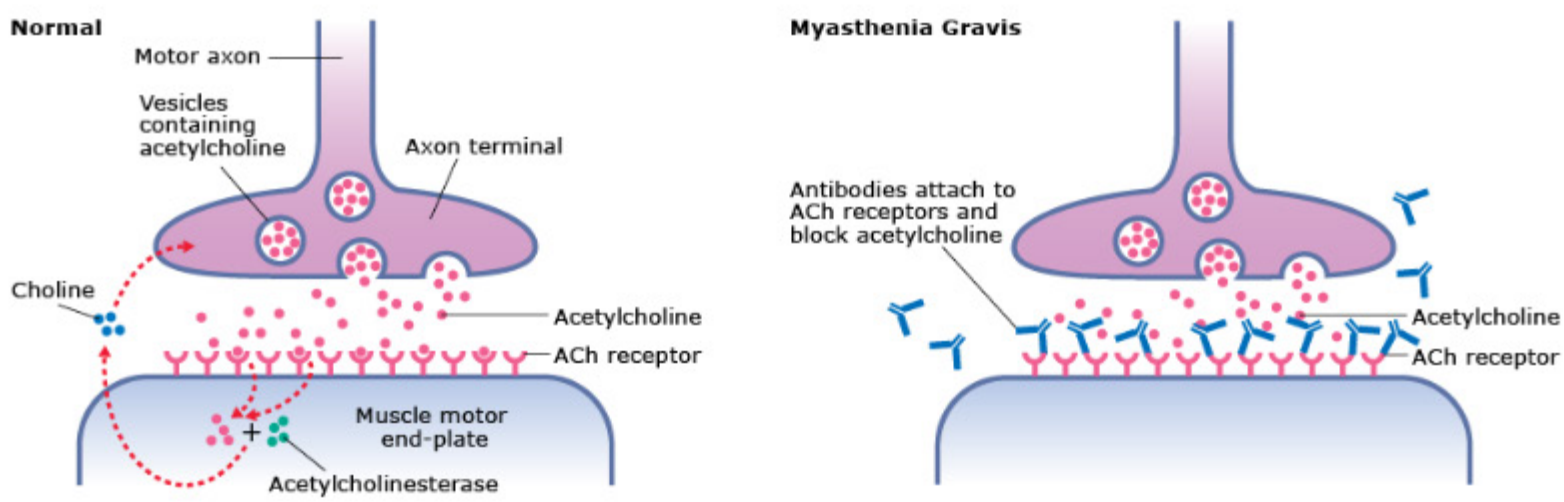
▲ **Figure 11-3.2C** Myasthenia Gravis



▲ **Figure 11-3.2D** Pathogenesis of Graves Disease (Type II) vs. Hashimoto Thyroiditis (Type IV)



▲ **Figure 11-3.2E** Pathogenesis of Myasthenia Gravis

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4 Type III Hypersensitivity

Type III hypersensitivities result when circulating complexes of antigen and antibody lodge in small diameter blood vessels and activate complement to cause inflammation.

4.1 Mechanism

These hypersensitivities may be autoimmune or directed against foreign antigens. The key difference between Type II and Type III hypersensitivities is that the damage Type III causes is system-wide, injuring small diameter blood vessels when they become plugged with complexes of antigen and antibody. Once the immune complexes lodge in the vasculature, they activate complement in that location that may be quite distant from their point of origin. These hypersensitivities tend to be causes of vasculitis with fibrinoid necrosis.

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▲ **Figure 11-4.2A** Lupus

4.2 Common Type III Hypersensitivities

▼ **Table 11-4.2A** Type III Hypersensitivities

Disease	Antigen	Manifestations
Arthus reaction	Any injected protein	Local pain and edema
Systemic lupus erythematosus	dsDNA, Sm, other nucleoproteins	Nephritis, arthritis, vasculitis, malar rash
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigens	Nephritis, granular or "lumpy bumpy" deposits
Serum sickness	Several proteins	Arthritis, vasculitis, nephritis
Polyarteritis nodosa	Hepatitis B virus Ag	Systemic vasculitis

▼ **Table 11-4.2B** Autoantibodies Associated with Hypersensitivity Diseases

Autoantibody	Disease Association
Anti-DNA, Anti-Sm	Systemic lupus erythematosus
Anti-Scl-70 (topoisomerase 1)	Scleroderma
Anti-centromere	CREST
Anti-histone	Drug-induced lupus
Anti-SS-A (Ro), SS-B (La)	Sjögren syndrome
Anti-U1/U2 RNP	Mixed connective tissue disease
Anti-Jo-1	Polymyositis/dermatomyositis

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▲ **Figure 11-4.2B** Scleroderma

Dr. P. Marazzi/Science Source

▲ **Figure 11-4.2C** CREST

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5 Type IV Hypersensitivity

Also known as *delayed type hypersensitivity*, Type IV hypersensitivity is a cell-mediated immune response that takes 48 to 72 hours to develop.

5.1 Mechanism

In Type IV hypersensitivities, a sensitized Th1 or Th17 cell is the root of the problem. At the effector cell level, damage may be caused by CD8+ Tc cells, macrophages activated by IFN-γ, or neutrophils activated by IL-17 and IL-23.

Dr. Ken Greer/Visuals Unlimited, Inc.

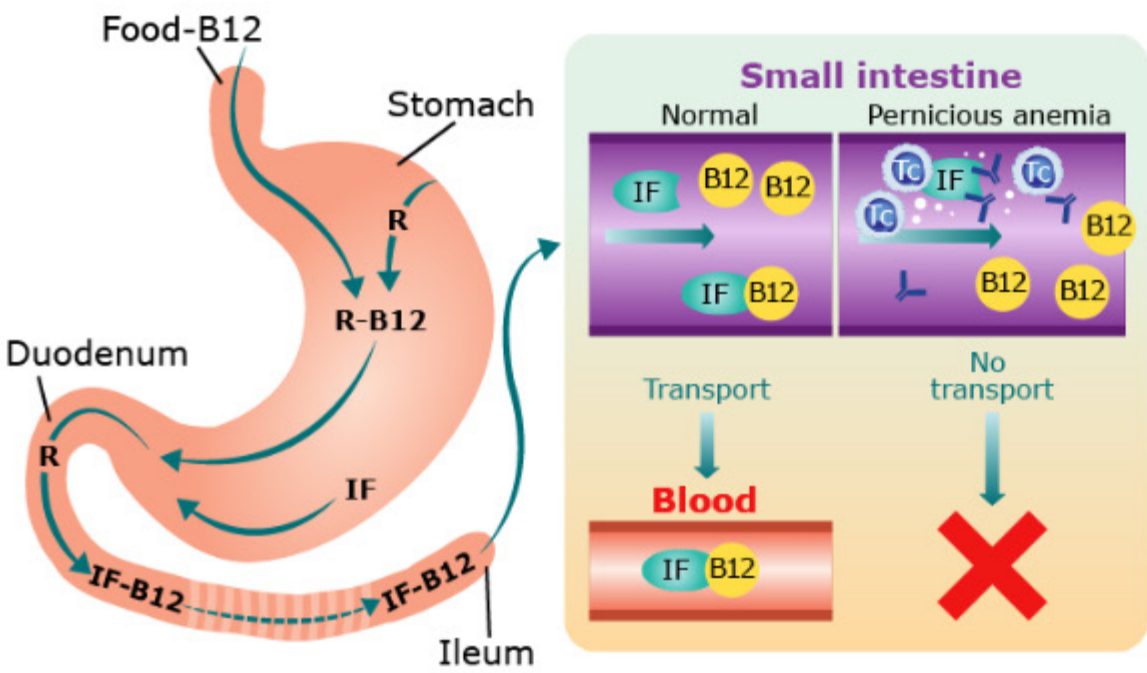
▲ **Figure 11-5.2A** Rheumatoid Arthritis

5.2 Common Type IV Hypersensitivities

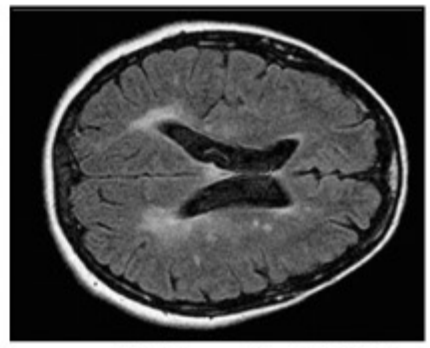
▼ **Table 11-5.2** Type IV Hypersensitivities

Disease	Specificity of Th1 Cells	Manifestations
Tuberculin test	Tuberculin and mycolic acid (PPD)	Granuloma at injection site
Contact dermatitis	Hapten/carrier responses to nickel, poison ivy or oak, catechols	Itching vesicular lesions
Rheumatoid arthritis*	Antigen in synovium (type II collagen?)	Destruction of articular cartilage and bone, chronic inflammation, rheumatoid factor (IgM against autologous IgG Fc region)
Hashimoto thyroiditis*	Thyroid antigen	Hypothyroidism due to Tc killing
Multiple sclerosis	Myelin basic protein	Progressive demyelination, paralysis
Pernicious anemia	Intrinsic factor, parietal cells	Neutralization of intrinsic factor, decreased vitamin B12 absorption, megaloblastic anemia
Type 1 diabetes (insulin-dependent)*	Insulin, glutamic acid decarboxylase, islet cells	Polydipsia, polyuria, polyphagia
Guillain-Barré syndrome*	Peripheral nerve gangliosides or myelin	Ascending paralysis, peripheral nerve demyelination
Crohn disease	Unknown antigen, commensal bacteria?	Chronic intestinal inflammation, obstruction
Celiac disease	Gliadin, Tc cells sensitized to MHC class 1-like molecule	Gluten-sensitive enteropathy

* Type IV hypersensitivity pathologies in which autoantibodies are used for diagnosis



▲ **Figure 11-5.2C** Pernicious Anemia



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▲ **Figure 11-5.2B** Brain Scan—Multiple Sclerosis

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6 Pathogenesis of Autoimmunity

The basis of autoimmune disease is a *failure of self-tolerance*. There are genetic, environmental, hormonal, and infectious triggers.

6.1 Mechanism

Tissue injury may serve as an inciting feature, exposing antigens that would normally be hidden. *Molecular mimicry* between host cells and invading microbes is often implicated in the early stages of disease. Because the immune response remains activated until the antigen is destroyed, when the antigen is "self," the damage is chronic and progressive.

6.2 HLA Associations With Disease

One of the strongest associations with autoimmunity is HLA type. The inheritance of a particular HLA haplotype does not mean the individual will develop the associated autoimmune disease; it only increases the relative risk.

▼**Table 11-6.2** HLA Disease Associations

Disease	HLA Association
Ankylosing spondylitis, psoriasis, IBD, Reiter syndrome	B27
Primary hemochromatosis	A3
Graves disease	B8
Goodpasture syndrome, MS	DR2
Systemic lupus erythematosus	DR2/DR3
Rheumatoid arthritis, pemphigus vulgaris	DR4
Type 1 diabetes	DR3/DR4
Celiac disease	DQ2/DQ8

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7 Therapy of Hypersensitivities and Autoimmune Diseases

Therapy of hypersensitivity-mediated disease is usually directed at modification of T cell function:

- Inhibition of proliferation (cyclosporine)
- Inhibition cytokine synthesis (corticosteroids)
- Destruction of all T cells (cyclophosphamide)

Newer therapies such as monoclonal antibodies or binding proteins are being developed that have more selective activity in destruction of only those cells involved with the injury.

▼Table 11-7.0A Monoclonal Antibody Therapies

Antibody	Clinical Uses
Abciximab	Anti-platelet, antagonist of IIb/IIIa receptors
Infliximab	RA and Crohn disease, binds TNF
Trastuzumab	Breast cancer, antagonist to ERB-B2
Eculizumab	Paroxysmal nocturnal hemoglobinuria, blocks C5 convertase
Dacliximab, basiliximab	Kidney transplant, blocks IL2R
Muromonab	Kidney transplant, blocks CD3
Rituximab	Non-Hodgkin lymphoma, binds CD20
Palivizumab	Respiratory syncytial virus, blocks fusion protein

Monoclonal antibodies (MAbs) are produced by fusion of myeloma cells (immortal in culture) and antigen-specific lymphocytes. Although this is a laborious laboratory procedure, screening of these random fusions for cells that produce useful antibodies has produced monospecific antibodies from immortal cultured cells that have the advantage of producing very specific results in the patient.

▼Table 11-7.0B Summary of Type I–IV Hypersensitivities

Type	Antibody	Complement	Cells	Examples
I (immediate)	IgE	No	Basophils and mast cells	Hay fever, insect venom sensitivity, anaphylaxis, asthma
II (cytotoxic)	IgM, IgG	Yes	PMN, ADCC cells	HDNB, transfusion reactions, hyperacute graft rejection, Goodpasture syndrome, rheumatic fever
II (non-cytotoxic)	IgG	No	None	Graves disease, myasthenia gravis, type 2 diabetes
III (immune complex)	IgM, IgG	Yes	PMN, macrophages	SLE, post-streptococcal glomerulonephritis, Arthus reaction, serum sickness, polyarteritis nodosa
IV (delayed-type)	None	No	Th1 cells, Tc, macrophages	TB test, MS, RA, Hashimoto thyroiditis, contact dermatitis, pernicious anemia, GVHD, type 1 diabetes, Crohn disease, celiac disease

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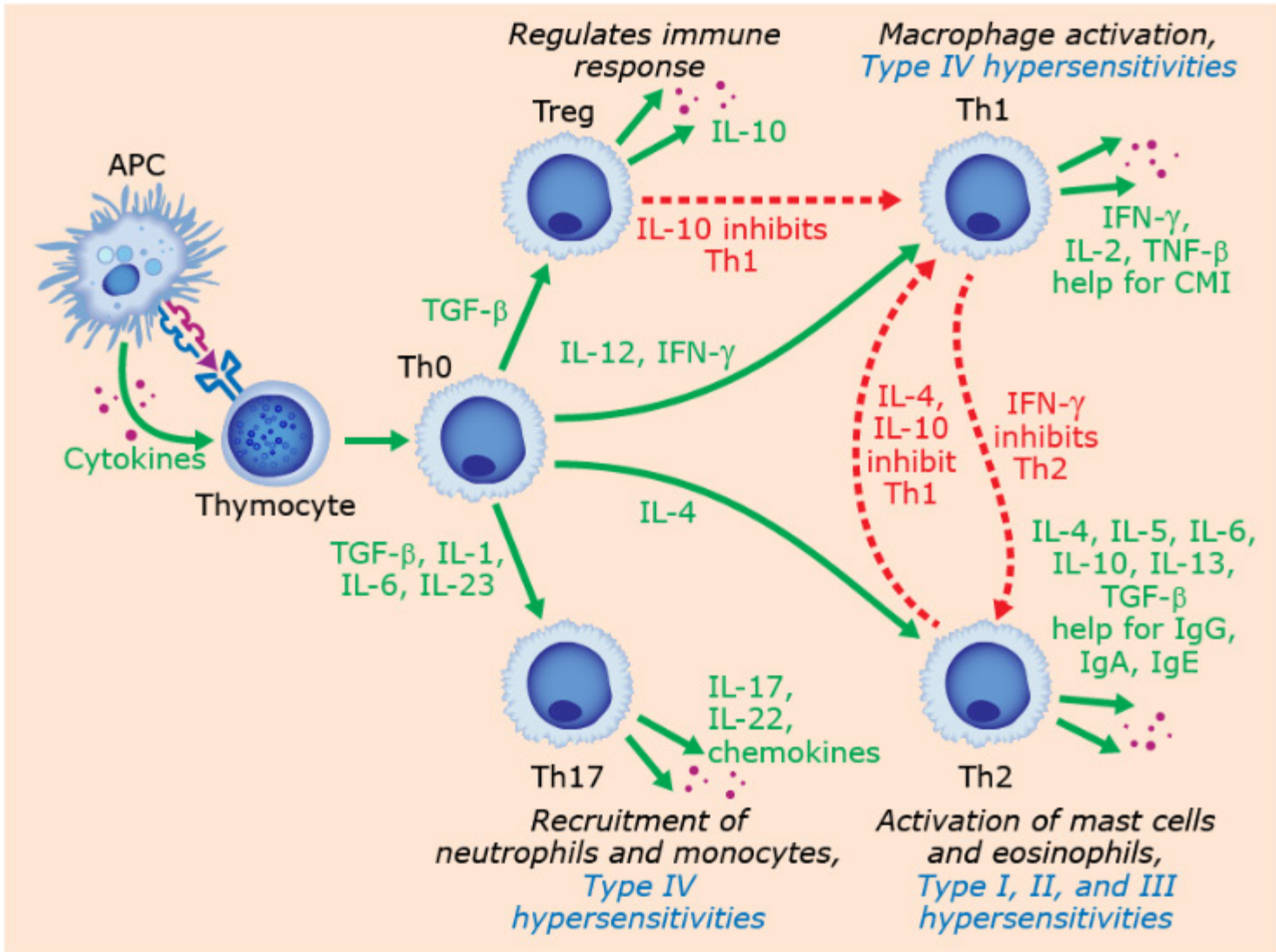

▲ **Figure 11-7.0** Helper T Cells and Hypersensitivities

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1 Overview of Transplantation Immunology

Transplantation involves moving cells or tissues from one individual to another. *Transfusion* is the special case in which blood products are delivered from *donor* to *recipient*. It has been practiced for many decades with relative ease because of the absence of MHC molecules on the surface of red blood cells. The problem with all other forms of transplantation, therefore, is the existence of the highly evolved self versus nonself recognition system (the MHC), which serves as a powerful, unfortunate signal that the transplanted tissue is an invader.

The forms of transplantation used today in medicine are:

- **Autografts:** Tissue moved from one location to another in the same individual, as in skin grafting, coronary artery replacement, etc.
- **Isografts (syngeneic grafts):** Tissue transplanted between monozygotic twins.
- **Allografts (allogeneic grafts):** Tissue transplanted between nonidentical members of one species.
- **Xenografts (xenogeneic grafts):** Tissue transplanted across species barriers, such as heart valves from a pig transplanted into a human.

USMLE® Key Concepts

For Step 1, you must be able to:

- Define the types of transplantation used in medicine today.
- Explain the molecular basis of graft rejection phenomena.
- Identify the basics of tissue compatibility testing.
- Describe the strategies for avoidance of graft rejection.

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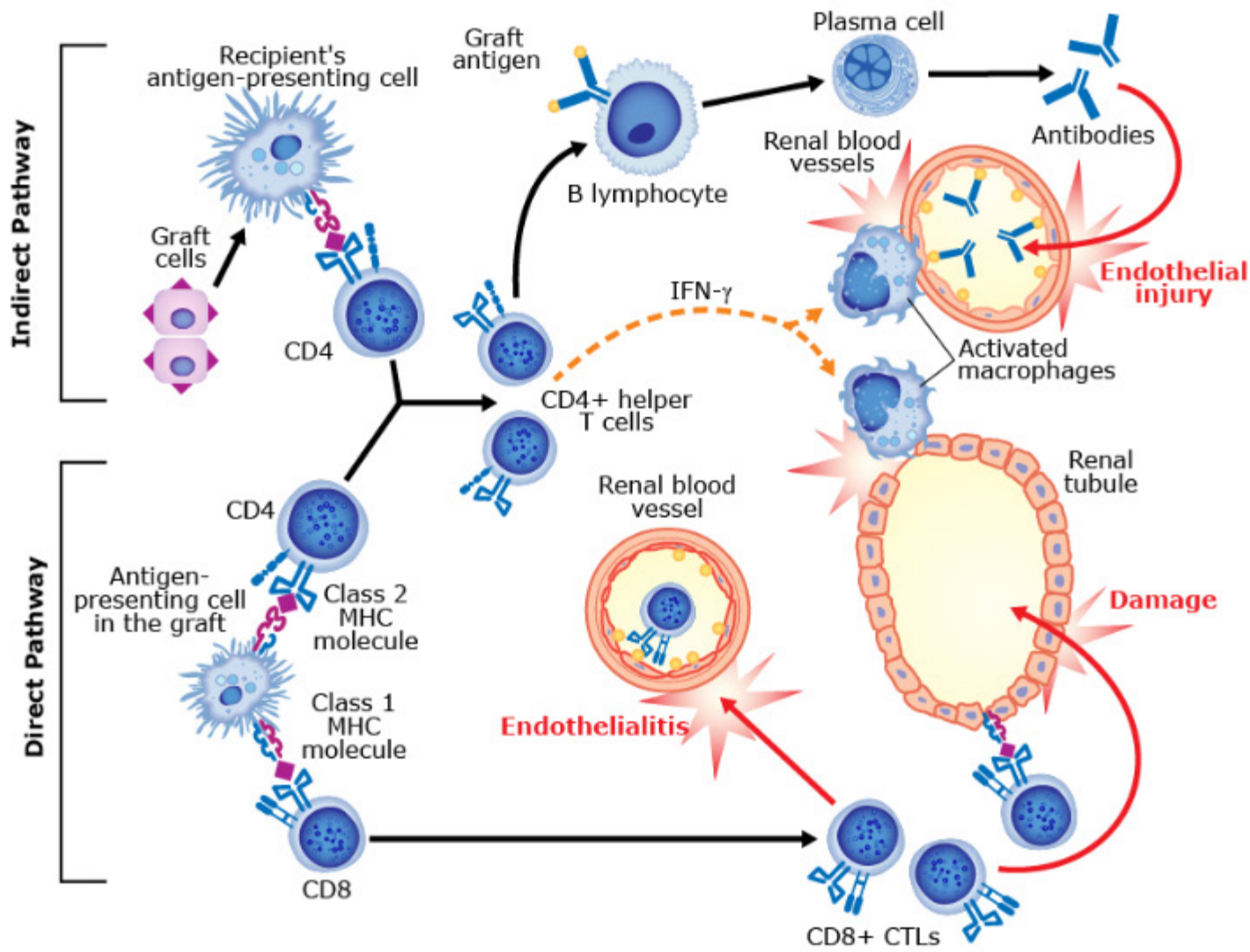
2 Mechanisms of Transplant Rejections

Because the HLA system is the most polymorphic genetic system in the human species, and because the molecules are expressed in a codominant fashion, it is inevitable that, in the absence of immunosuppression, all grafts except autografts will eventually be recognized and destroyed by the process of *graft rejection*. Even isografts between monozygotic twins are subject to rejection since minor mutational changes that occur during gestation and development can ultimately cause the transplanted tissue to be recognized as foreign.

The initial stimulation to reject transplanted tissue can occur via direct or indirect pathways:

- **Direct pathway:** Here, donor antigen-presenting cells in the graft serve as the stimulus for nonself recognition, since the molecules themselves, with or without the presence of abnormal peptides for presentation, can be recognized as foreign.
- **Indirect pathway:** Here, it is the recipient's antigen-presenting cells that process and present the debris of dead cells from the engrafted tissue to activate recipient Th cells.

In either pathway, once antigen presentation to Th cells occurs, both humoral and cell-mediated arms of the immune response are activated.



▲ **Figure 12-2.0** Transplant Rejection

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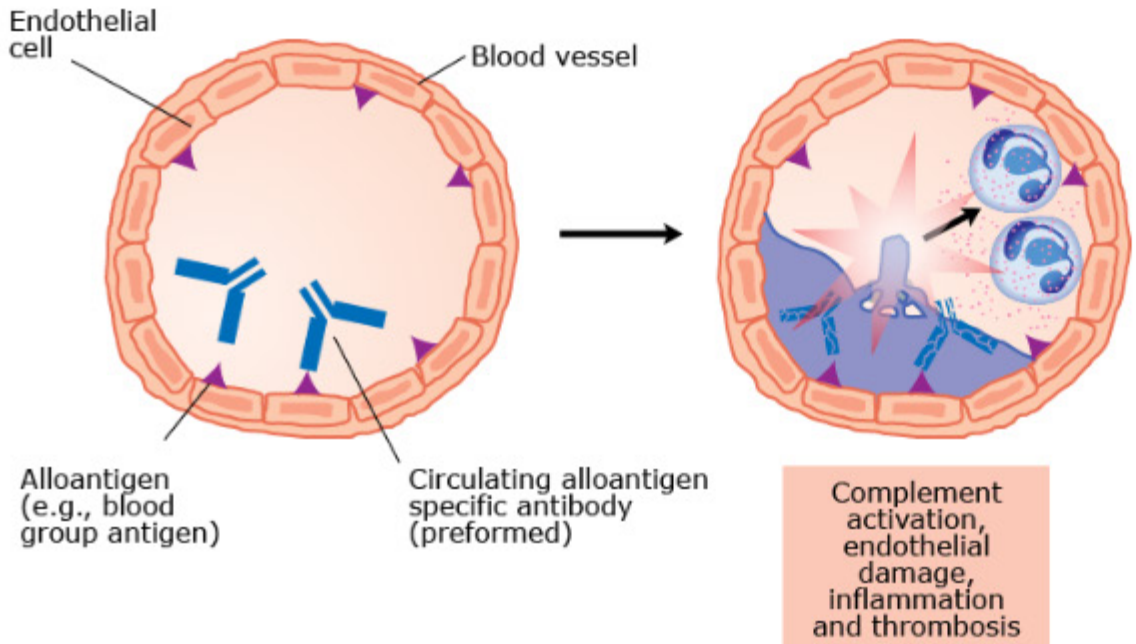
2.1 Types of Host vs. Graft Rejection

The different mechanisms of host-versus-graft rejection are classified according to their time of onset and the type of effector mechanism activated.

2.1.1 Hyperacute Rejection

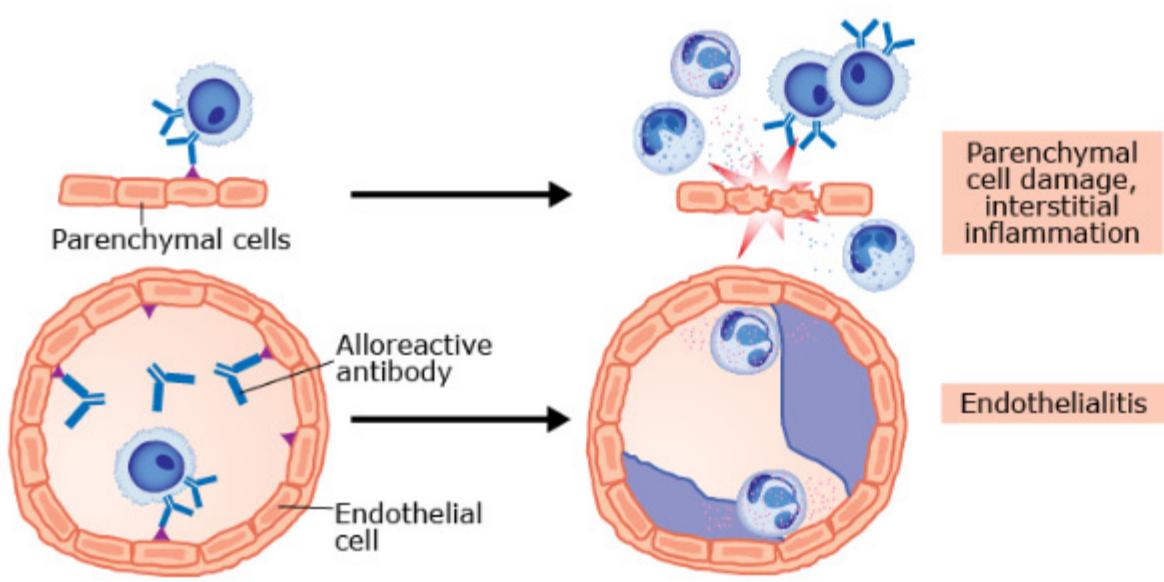
Hyperacute rejection becomes manifest within minutes to hours of the transplant. It is a result of preexisting antibodies of the recipient immediately attacking the donated tissue. This can happen in cases of *ABO blood type incompatibility* or *failure to cross-match* the cells and serum of donor and recipient.



▲ **Figure 12-2.1A** Hyperacute Rejection

2.1.2 Acute Rejection

Acute rejection manifests days to weeks following transplantation. With the availability of strong immunosuppressive therapies, this form of rejection has become quite rare, but the mechanism involves the *sensitization of Th cells* via either the direct or indirect pathways and production of humoral or cell-mediated mechanisms of defense. Untreated, the graft suffers parenchymal cell damage, interstitial inflammation, and endothelialitis.



▲ **Figure 12-2.1B** Acute Rejection

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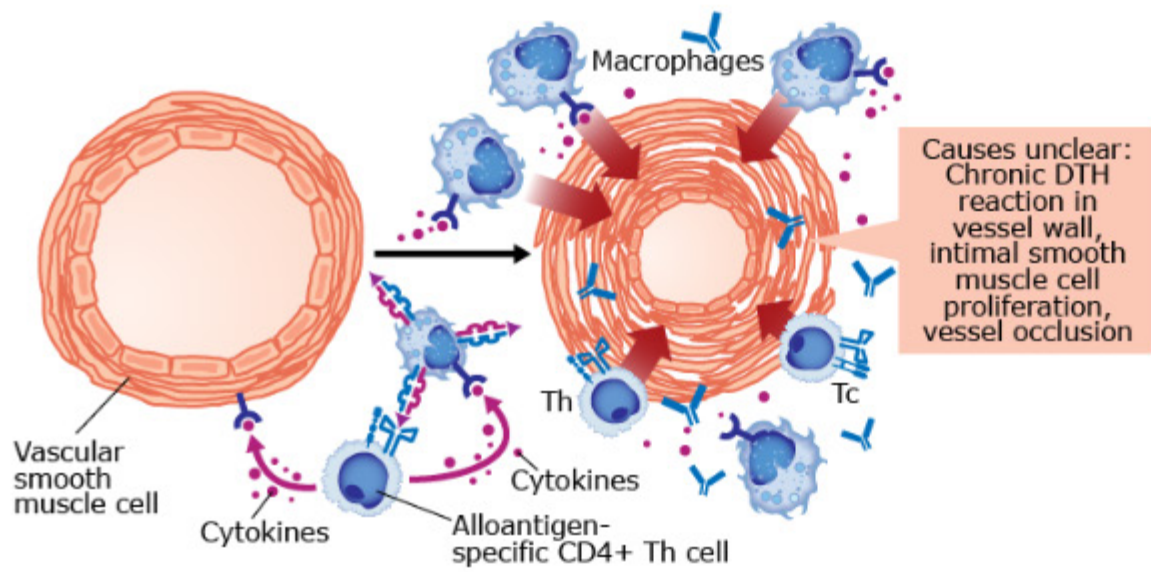
2.1.3 Accelerated Acute Rejection

Accelerated acute rejection occurs within days of transplantation surgery—when the failure of a first graft necessitates a second. This is a reflection of the timing of a *memory response* against graft alloantigens, and can be avoided if all subsequent grafts have a different histocompatibility haplotype from the first one.

2.1.4 Chronic Rejection

Chronic rejection takes months to years to develop and is a result of the concerted attack of the entire immune response on the graft. The causes are multifactorial, but the chronic delayed-type hypersensitivity reaction in the vessel walls of the graft leads to intimal smooth muscle cell proliferation and ultimately to vessel occlusion.



▲ **Figure 12-2.1C** Chronic Rejection

2.2 Graft vs. Host Rejection

In the special case of transplantation of bone marrow, or more rarely in liver transplantation, it is possible for the donor T lymphocytes in the engrafted tissue to recognize the MHC of the recipient as foreign and mount an immune response in the reverse of those described above. This special case of rejection is called *graft versus host disease (GVHD)*, and depends on the ability of the engrafted T cells to multiply to a number that becomes life threatening to the recipient. The manifestations of this reaction include death of any rapidly proliferating cell population (epithelia and mucosa) and the resultant rash, jaundice, diarrhea, and gastrointestinal hemorrhage.

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Clinical Application

The ability of an immune response to clone itself depends on the Th cytokine interleukin-2. In the setting of graft rejection, the ability of an incipient rejection response to become amplified in this way can become life-threatening. Therefore, many strategies to avoid transplant rejection involve the attempt to minimize IL-2 production. In the first place, in choosing appropriate donor-recipient pairings when possible, *it is best to match individuals at the MHC class 2 loci first*. Although this seems counterintuitive since killer recognition involves MHC class 1 presentation, the production of IL-2 for cloning occurs at the level of MHC class 2 presentation. If IL-2 synthesis can be avoided, at least any incipient immune response will not become amplified.

Two monoclonal antibody therapies based on this principle are now in use for prevention of acute graft rejection. *Basiliximab* and *Dacliximab* are both monoclonal antibodies that bind the *alpha chain of the high-affinity IL-2 receptor (CD25)* on the surface of activated T lymphocytes and diminish these cells' ability to clone themselves to dangerous levels without making the patient more susceptible to opportunistic infections.

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3 Tissue Compatibility Testing

Testing to determine the compatibility between donor and recipient is essential to minimize the severity of graft rejection and improve the likelihood of successful transplant. The four types of testing are: ABO blood grouping, cross-matching, MHC class 1 typing, and MHC class 2 typing.

3.1 ABO Blood Grouping and Cross-Matching

The first steps in identifying an appropriate organ match for a recipient are *ABO blood typing* and *cross-matching*. Failure to perform these two steps can result in the hyperacute rejection of the organ due to the failure to identify preexisting anti-donor antibodies in the recipient.

ABO blood group antigens are glycoprotein molecules found on the surfaces of all erythrocytes and endothelial cells. Antibodies against them are made naturally in response to sensitization to similar glycolipid molecules found on the surfaces of normal intestinal flora. Thus, patients naturally make *IgM isohemagglutinins* against any blood group alloantigen that is foreign to their own, but should be protected by self-tolerance from an immune response that would destroy their own red blood cells.

Cross-matching is done by mixing the serum of the recipient with cells from the prospective donor. If there are any yet-unidentified anti-donor antibodies that could cause graft failure, they will be identified with this assay.

	Blood Types			
	A	B	O	AB
Serum from **A** patient contains anti-B antibodies	N	A	N	A
Serum from **B** patient contains anti-A antibodies	A	N	N	A
Serum from **O** patient contains anti-A and anti-B antibodies	A	A	N	A
Serum from **AB** patient contains no antibodies to A or B	N	N	N	N

A = Agglutination
N = No Agglutination

▲ **Figure 12-3.1** ABO Blood Typing

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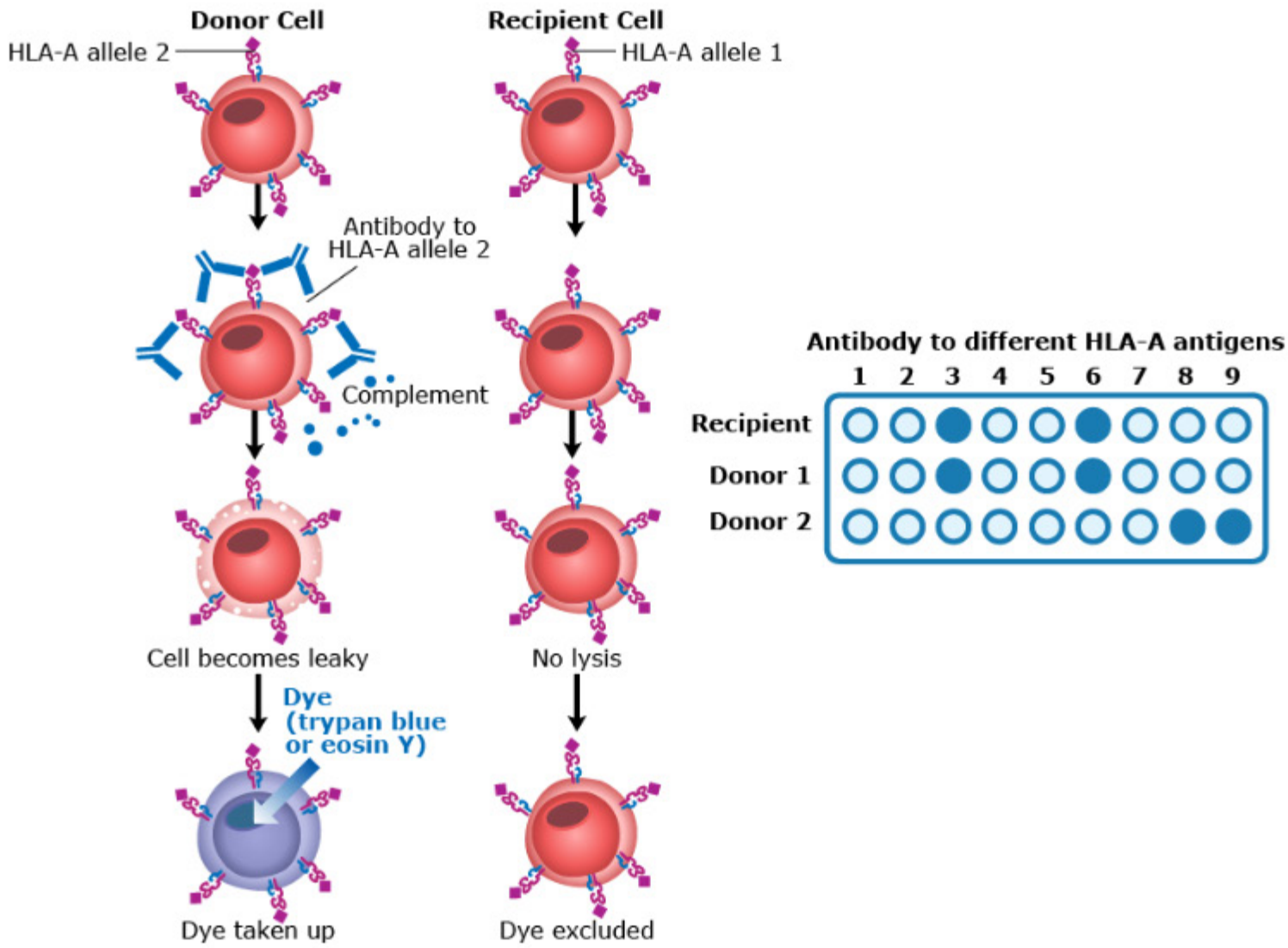
3.2 MHC Class 1 Typing

When patients awaiting transplant are critically ill, ABO blood typing and cross-matching may be the only tests possible in the limited time frame. However, in cases with potential living donors, HLA typing is subsequently undertaken. Three sets of alleles have been shown to have the strongest predictive value of graft success: *HLA-A, HLA-B,* and *HLA-DR*.

Identification of the MHC class 1 products is done either with a *microcytotoxicity test* (shown here) or with *flow cytometry* (see chapter 13).

In the microcytotoxicity test, batteries of antisera prepared against specific HLA-A or HLA-B alleles are sequentially mixed with lymphocytes from donor and recipient. If the chosen antibody finds its antigen on the surface of a cell, it binds so that when complement is subsequently added, the membrane becomes leaky and, with the final addition of a colored dye, the leaky cell takes up color. If the antibody tested fails to identify the surface molecule on the cell, this does not occur, and the cells remain transparent. Since each nucleated cell of donor and recipient wears two A molecules and two B molecules, this can be quite a laborious effort of trial and error until the two alleles are identified for each locus, for each individual.



▲ **Figure 12-3.2** Microcytotoxicity Test

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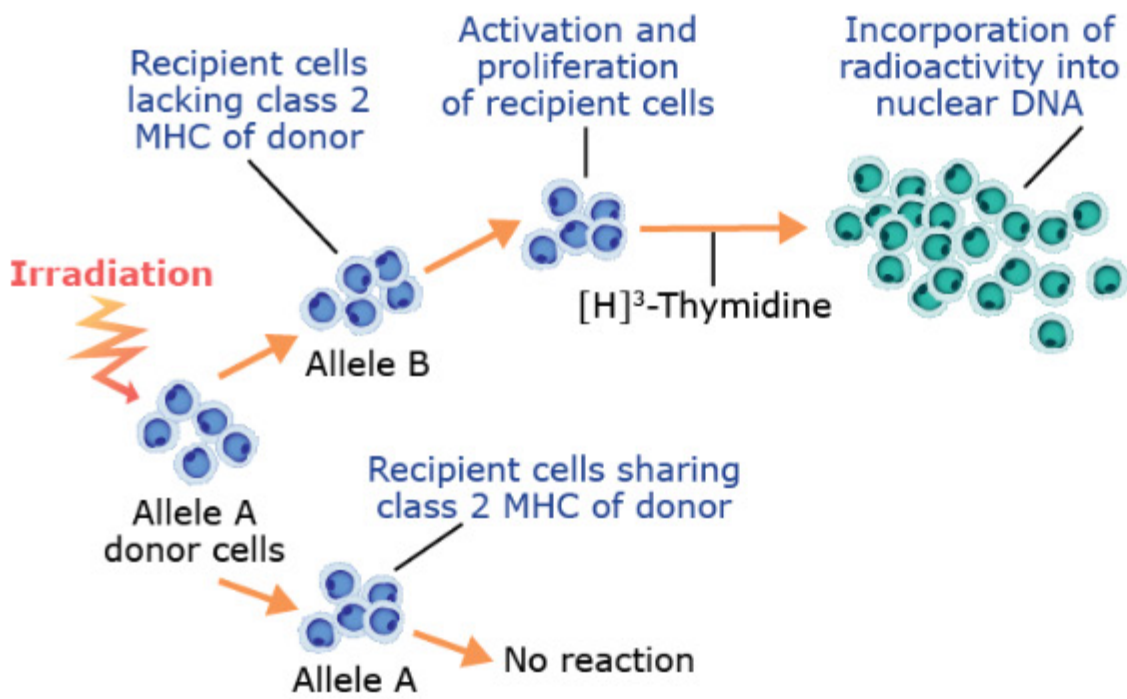
3.3 MHC Class 2 Typing

To identify MHC class 2 antigens, a microcytotoxicity test can be performed as above, or more commonly, a *mixed lymphocyte reaction (MLR)* is used. Since MHC class 2 presentation results in the production of IL-2, this is an assay that measures cell proliferation in response to mismatched alleles at these loci. For host versus graft settings, the peripheral blood leukocytes of the potential donor are irradiated to make them incapable of proliferation. This makes the assay a determination of cloning in one direction only: Is the recipient going to identify donor cells and make IL-2 or not? When normal peripheral blood leukocytes from the recipient are now added into the culture, any mismatch at the class 2 loci results in the production of IL-2, cloning of recipient cells, and incorporation of a radio-labeled nucleotide precursor into the newly replicating DNA. Therefore, any increase in radioactivity in the culture is a reflection of cell division, which is a bad sign. The best donor-recipient pairing is one in which no cell division is observed.



▲ **Figure 12-3.3** Mixed Lymphocyte Reaction (MLR)

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CHAPTER 13 Uses of Immunology in Diagnostic Medicine

1 Precipitation and Agglutination Reactions

When antigens and antibodies combine, they do so in relationship to the linkage of their combining sites. When very small complexes form, they remain in suspension or solution, but when the maximum number of combining sites for both antigen and antibody are engaged, the complexes become large and insoluble or fall out of suspension.

Many diagnostic tests depend on the observation of *precipitation or agglutination*. Both of these assays depend on very large complexes settling out of a liquid; the only difference between the two is that precipitation involves the settling of a protein antigen and agglutination involves the same thing but with a particulate antigen such as a red blood cell or a latex bead.

USMLE® Key Concepts

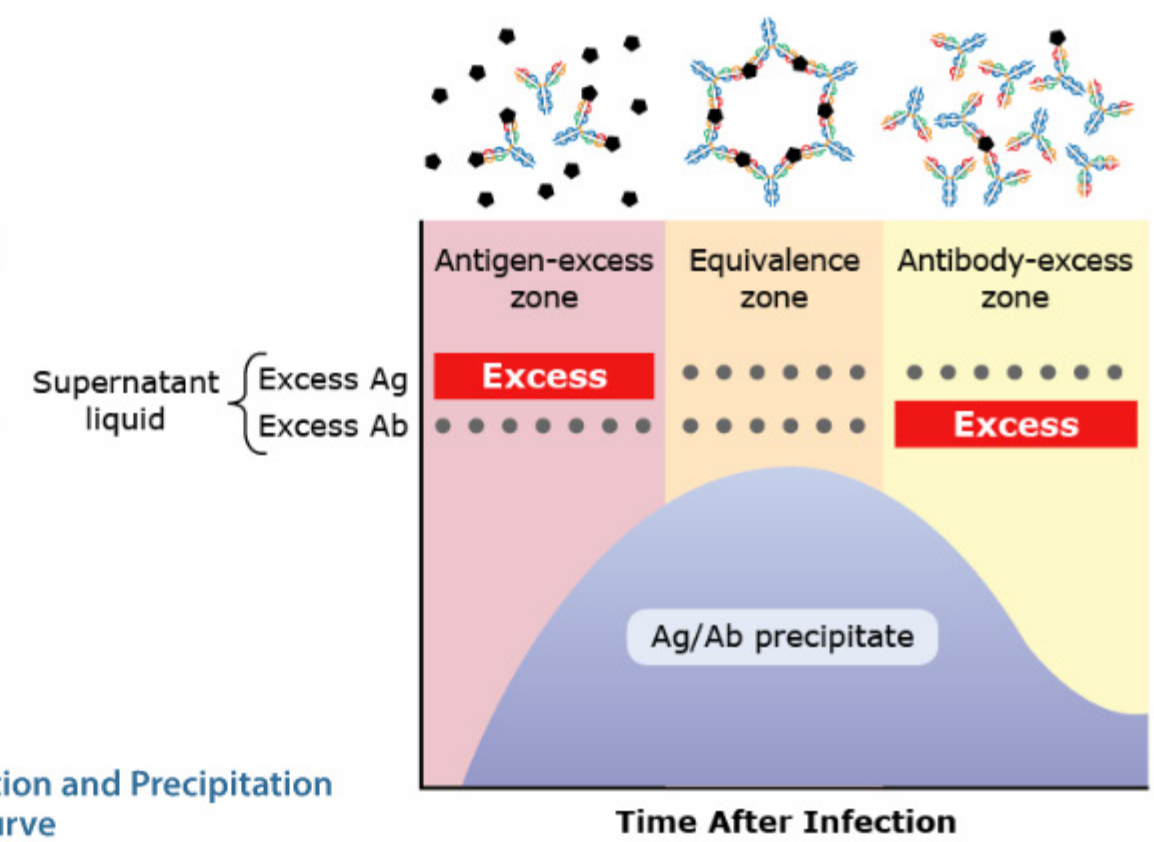
For Step 1, you must be able to:

- Describe the general procedures and uses for the most common immunologic tests in medicine.
- Explain how to interpret data from these sources to diagnose immune or microbial disease.

1.1 Precipitation and Agglutination Titration Curve

Making a precipitation or agglutination curve by titration of antibody against antigen can result in three states within the test tube. These are the same three states that also manifest in the serum of a patient confronting infection. Early in infection, the microbe is multiplying and the immune response has not yet begun, so in the supernatant liquid (or serum) one would measure an excess of antigen *(antigen excess zone)*.

As time passes and the patient begins to mount an immune response, a point is reached in which the perfect amount of antibody is being made to bind every molecule of antigen. At this point the patient enters the *equivalence zone* of the curve—during titration this would be the point at which the complexes become very large and settle out of the liquid. Within the equivalence zone, no excess molecules of antigen or antibody are found in the serum because they are all bound together and thus in the precipitate or agglutinate.



▶ **Figure 13-1.1** Agglutination and Precipitation Titration Curve

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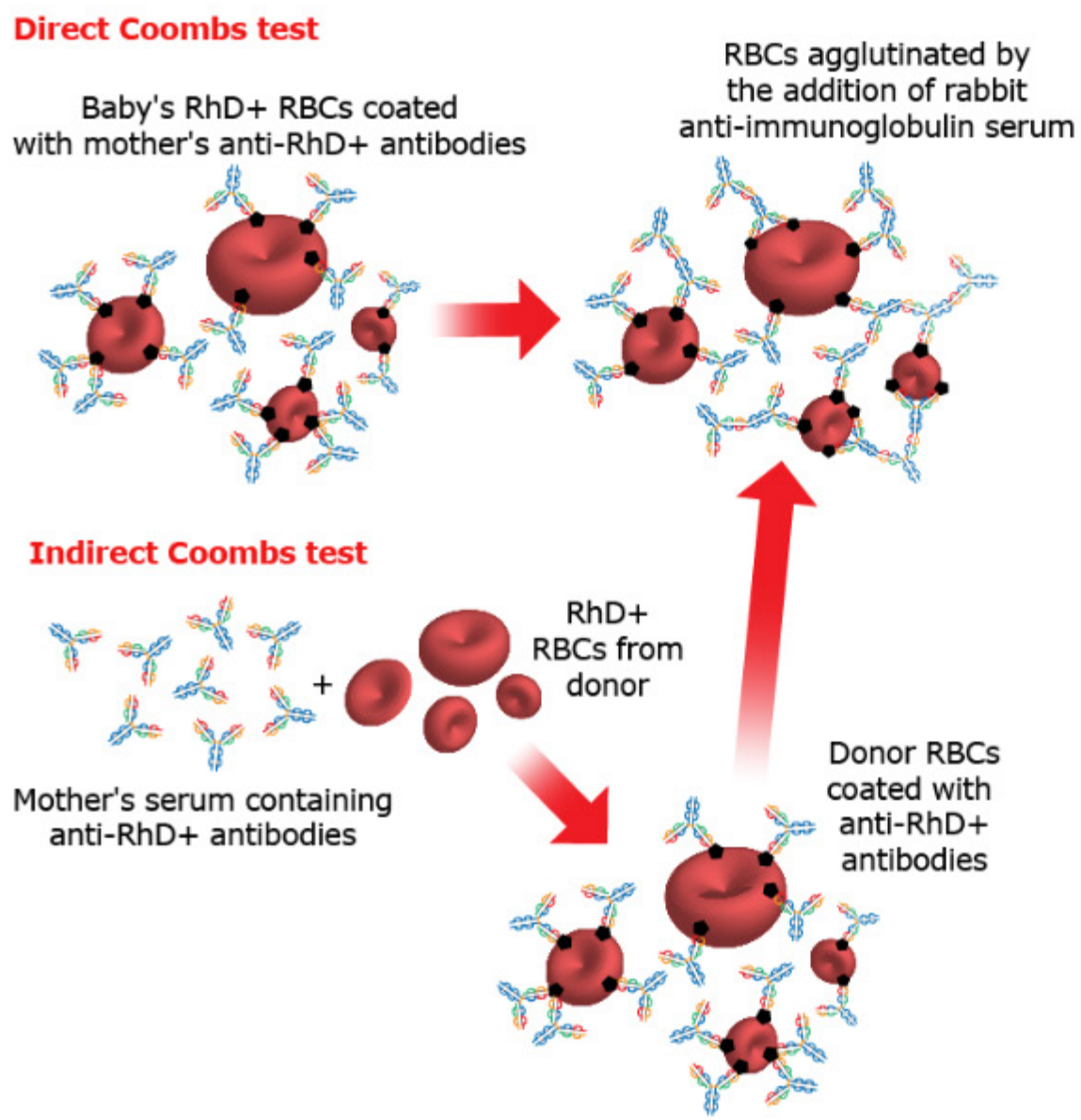
Finally, as the life cycle of the microbe is stopped by the immune response, the continuing secretion of antibodies causes the complexes to once again become small in size. In the serum, an excess of antibody *(antibody excess zone)* manifests by way of a rising titer of antimicrobial antibody.

1.2 Coombs Test

The *Coombs test* or *antiglobulin test* is an agglutination test used to diagnose the presence of IgG antibodies against red blood cells. The direct Coombs test or direct antiglobulin test is used to diagnose autoimmune hemolytic anemia. It is performed by taking a sample of blood from the patient, adding *antihuman globulin (Coombs serum)* and observing for agglutination.

The indirect Coombs test or indirect antiglobulin test detects free antibodies in a patient's serum. It is used prior to transfusions and for antenatal testing of pregnant women. It is performed by mixing the patient's serum with erythrocytes of known antigenicity, adding Coombs serum, and observing for agglutination.



▲ **Figure 13-1.2** Coombs Test

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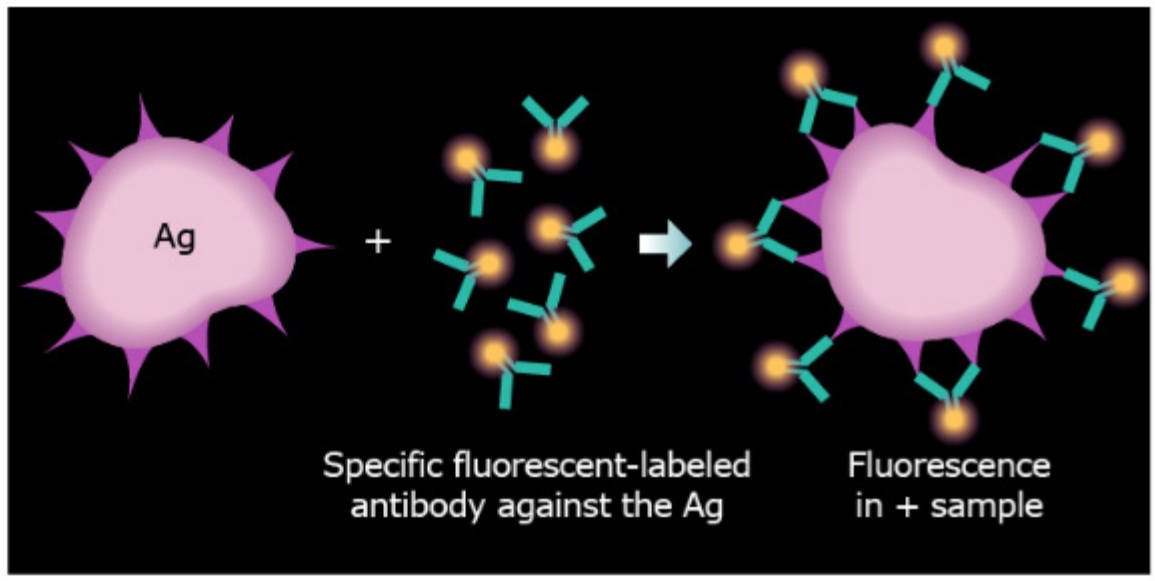
2 Immunofluorescent Assays

Immunofluorescent assays use microscopy to visualize the location and distribution of fluorescent dyes tagged to antibodies in blood and tissue samples.

2.1 Direct Fluorescent Antibody Test

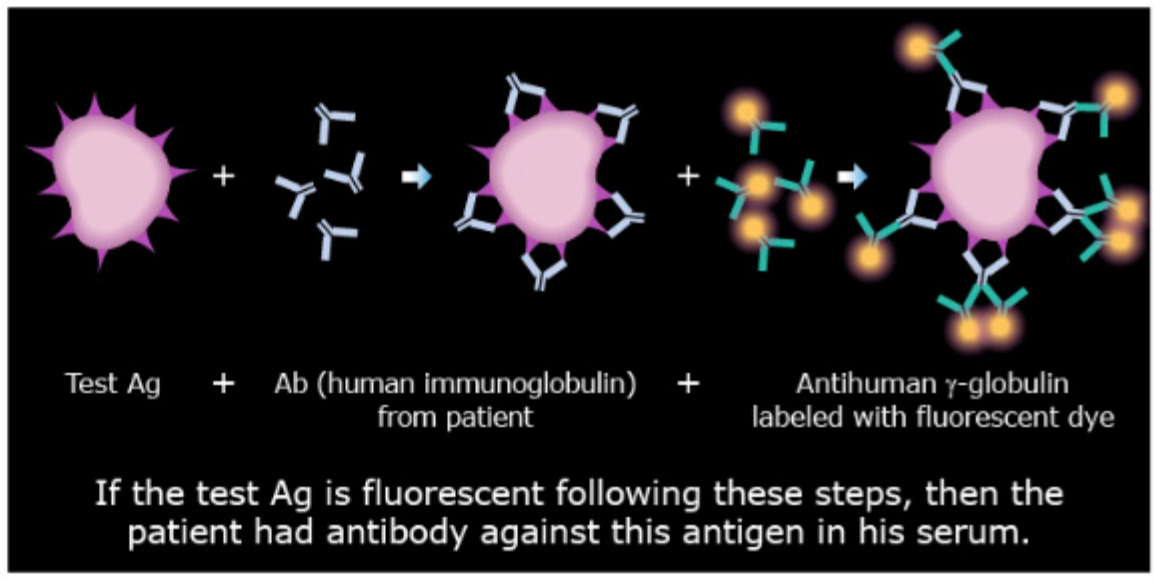
The *direct fluorescent antibody test (DFA)* is used to identify the presence of antigen in a patient. It is used in cases where the pathogen is difficult to visualize or difficult to culture. It is performed by treating a biopsy specimen with fluorescent-tagged antibodies against a microbe. If the tissue specimen fluoresces, then the diagnosis is established. Examples of the use of this test would include the diagnoses of *Chlamydia*, respiratory syncytial virus, herpes simplex viruses 1 and 2, and *Pneumocystis*.



▲ **Figure 13-2.1** Direct Fluorescent Antibody Test

2.2 Indirect Fluorescent Antibody Test

The *indirect immunofluorescent antibody test (IFA)* is used to detect the presence of antibody in a patient, so it is widely applied in the diagnosis of autoimmune disease. To perform this test, serum from the patient is incubated with a sample of tissue or cells expressing the antigens against which the patient is believed to be autoimmune. If the antibodies are present in the serum, they will bind to the tissue sample, so that subsequent addition of *antihuman globulin* that has been labeled with a fluorescent dye will cause the tissue to fluoresce. Diagnoses assisted with this test include Graves disease, Goodpasture syndrome, and systemic lupus erythematosus.



▲ **Figure 13-2.2** Indirect Fluorescent Antibody Test

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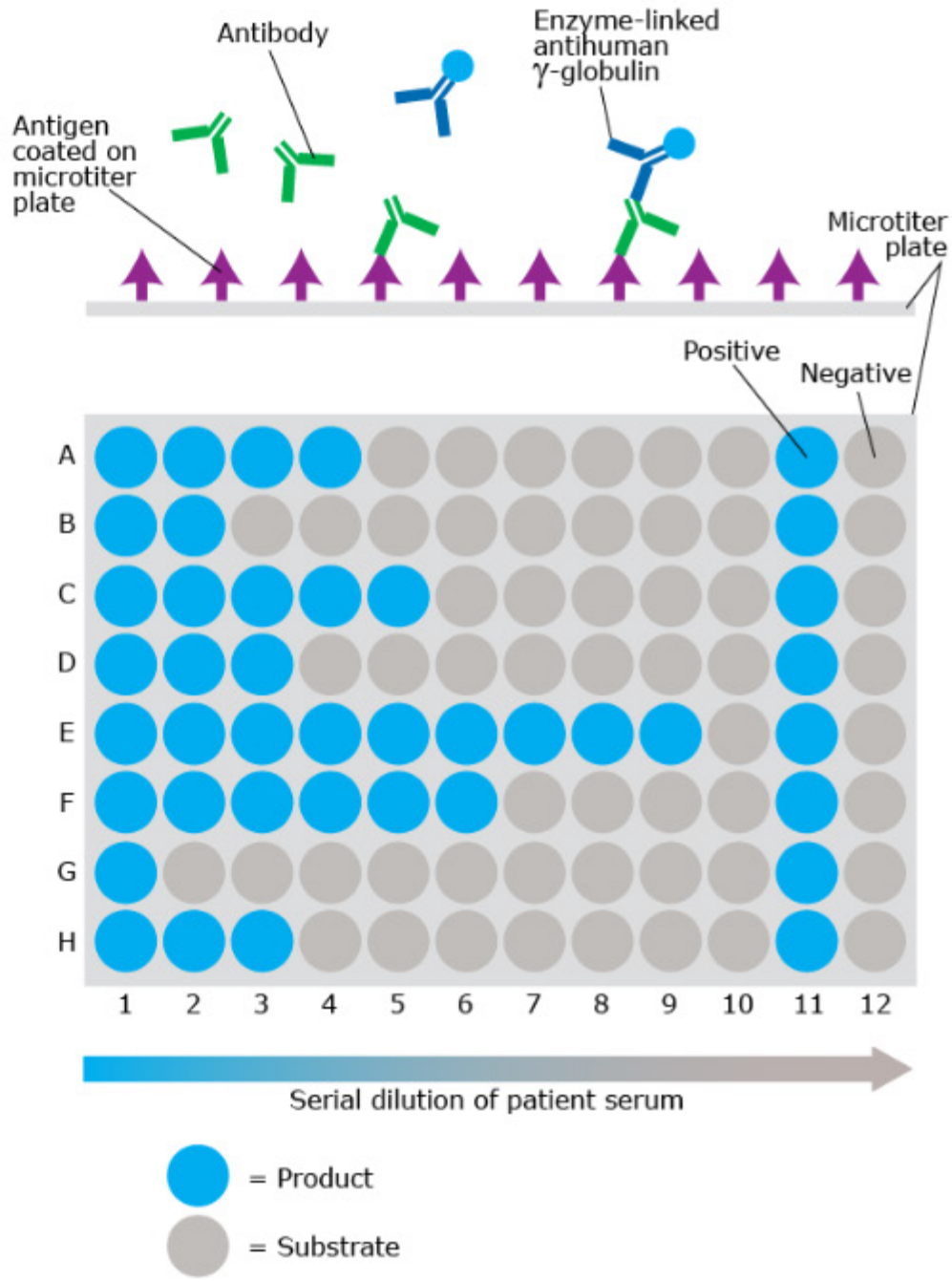
3 Radioimmunoassay (RIA) and Enzyme Immunoassay (EIA)

The *radioimmunoassay (RIA)* and *enzyme immunoassay (EIA)* are two of the most commonly used diagnostic techniques in medicine today. They are extremely sensitive, detecting as little as 10^{-9} g of material, but differ in the means of visualizing the result. In the case of EIA, an enzyme causes color change as the result, and in the RIA, changes in radioactivity are detected. An EIA is used as the screening test for HIV infection.

In such testing, the viral p24 antigen is bound to the wells of a microtiter plate, and a serial dilution of patient sera is added to each of the wells. This is followed by washing to remove unbound antibodies, treatment with an enzyme-linked antihuman globulin, repeat washing, and finally the addition of the substrate for the enzyme. Any color change in the well reflects that these binding reactions have all occurred in sequence, and that the patient has a *titer* (defined as the reciprocal of the serum dilution in the last positive well) of antibody to that viral antigen.



▲ **Figure 13-3.0** Enzyme Immunoassay

The problem with these tests is their extreme sensitivity. In the case of HIV screening, there are so many false positives on the EIA that it must always be confirmed by the Western blot, and no patient should be informed that he has HIV infection unless both the EIA and Western blot are positive. The *radioallergosorbent test (RAST)* is an example of an RIA that detects IgE antibodies in allergic individuals.

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4 Western Blot

The *Western blot (protein immunoblot)* is a common adjunct to the EIA to make a strong predictive pairing for diagnosis in cases in which the EIA suffers from large numbers of false positives. Examples of its use include HIV and Lyme disease diagnosis.

In the Western blot for HIV confirmation, the viral antigens are separated by electrophoresis in gel, and the bands are blotted onto nitrocellulose filter paper. The filter paper is then bathed in serum from the patient with the positive EIA results, and finally a visualizing method is used. In some cases, an enzyme-linked antihuman globulin is added, and the substrate color change is noted. In other cases, a radioactive antihuman globulin is added, and the results are read on radiographic film.

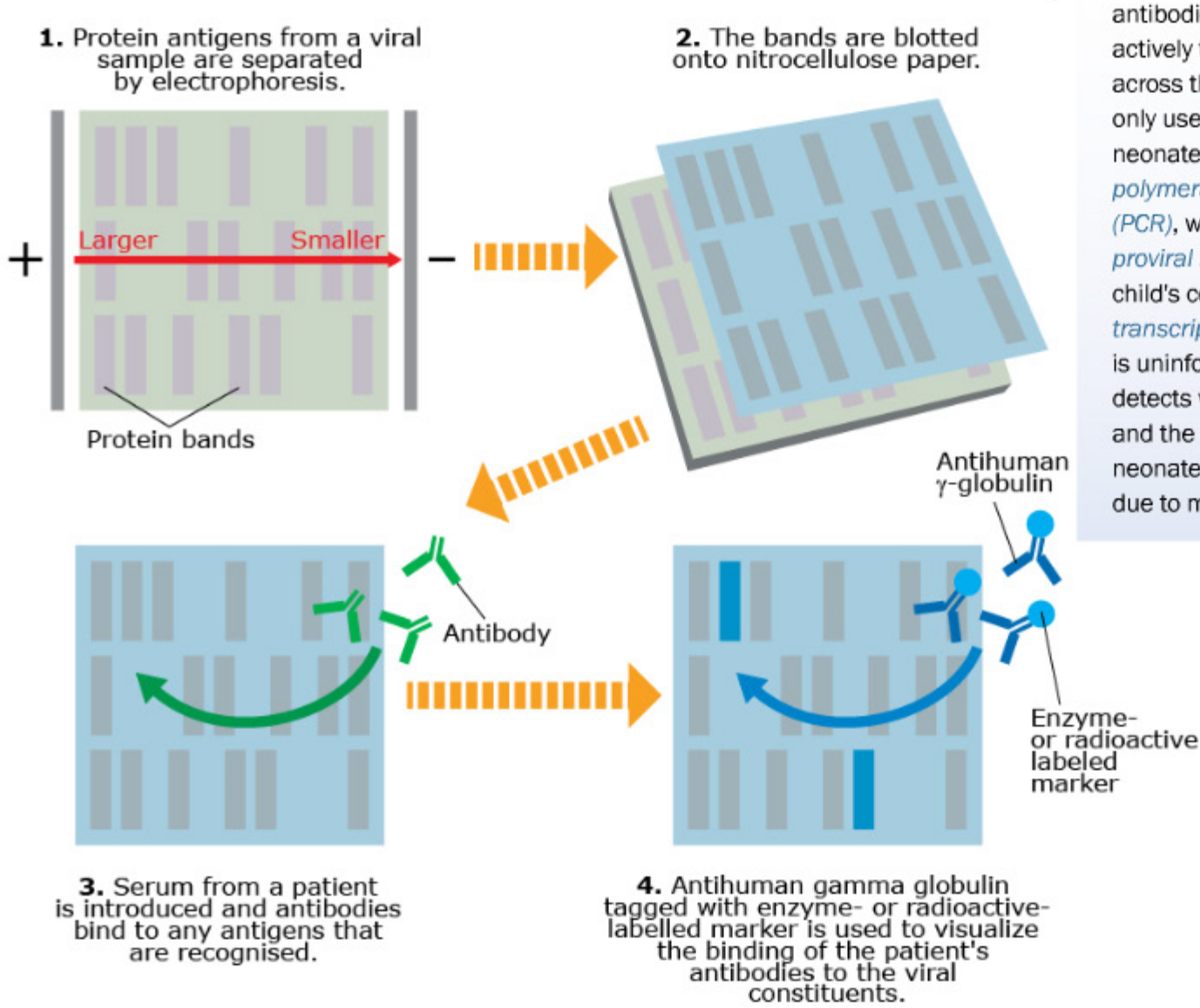
In the case of HIV infection confirmation, it is necessary to find at least *two positive bands, gp41, gp120* and/or *p24*. Fewer than two bands, or positive bands other than those mentioned, cause the result to be defined as inconclusive.

Connection to Biochemistry

- Western blot (protein immunoblot): detects protein
- Northern blot: detects RNA
- Southern blot: detects DNA

Clinical Application

Infants born to HIV+ mothers cannot be diagnosed using either the EIA or the Western blot because maternal antibodies have been actively transported across the placenta. The only useful diagnostic for neonates in this case is the *polymerase chain reaction (PCR)*, which detects *proviral DNA* inside the child's cells. Even *reverse transcriptase PCR (RT-PCR)* is uninformative since it detects virus in the blood, and the viral load in the neonate is extremely low due to maternal antibodies.



▲ **Figure 13-4.0** Western Blot Test

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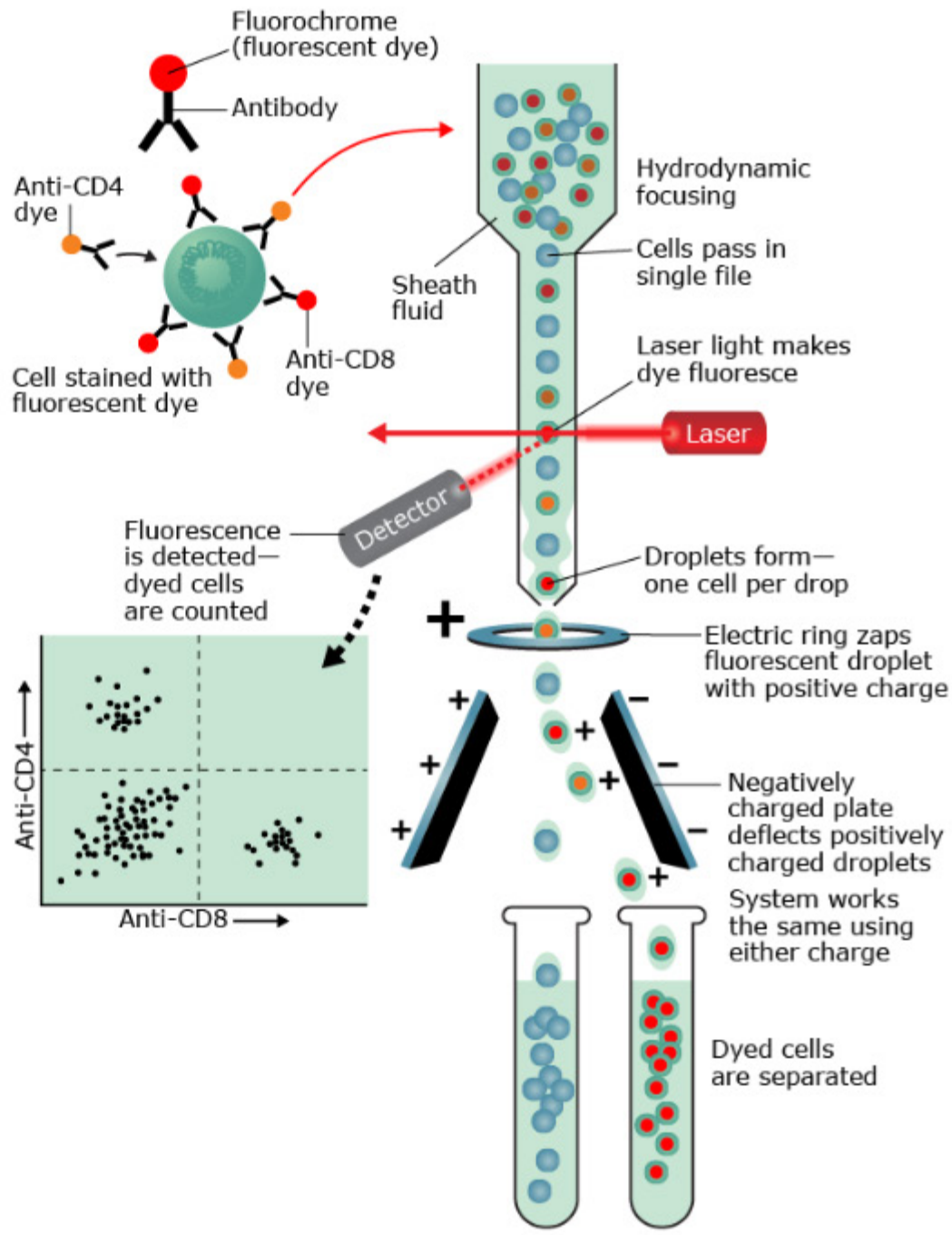
5 Fluorescence-Activated Cell Sorter

The *fluorescence-activated cell sorter (FACS)* is a computer-driven instrument used to analyze complex mixtures of cells. First, the cells are labeled with antibodies wearing fluorescent tags. Each antibody has a different color of fluorescent dye. As the cells are passed through the apparatus in a single file, the FACS measures the intensity and color of fluorescence on each cell and makes a dot on the graph to reflect that measurement. An accumulation of dots in a particular area on the graph indicates a large number of cells with that characteristic.

Each graph generated compares two colors of dye, and the color intensity is graphed vertically on the y-axis (bottom to top) or horizontally on the x-axis (left to right). Thus, cells that have below-threshold fluorescence with both dyes are marked in the lower left quadrant, cells that have only one dye are marked as high on the y-axis or far to the right on the x-axis, and cells that wear both dyes are in the upper right quadrant (high on the y-axis and far right on the x-axis).



▲ **Figure 13-5.0** Flow Cytometry With FACS

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Chapters 11–13 Review Questions

1. A 42-year-old scout leader reports to his doctor with an itchy rash on his right calf. He reports being on a campout three days ago with his scout troop. Physical examination reveals a red, vesicular rash on the outer aspect of the right lower leg. Which of the following is the cause of this rash?

A. B lymphocytes
B. Neutrophils
C. Plasma cells
D. Th1 lymphocytes
E. Th2 lymphocytes

2. A 60-year-old male presents to his physician complaining of pain in his wrist, hand, and knee joints associated with swelling, tenderness, and heat. Laboratory studies reveal a normocytic, normochromic anemia with an elevated erythrocyte sedimentation rate. Serum is positive for IgM antibodies against autologous IgG. A sample of synovial fluid from the affected joints is most likely to reveal which of the following?

	Protein	IgM	TH17 lymphocytes	IL-1	TNF
A.	Normal	↑	↑	↑	↑
B.	↑	↑	↑	↑	↑
C.	↑	Normal	↑	↑	↑
D.	Normal	Normal	↓	↓	↓
E.	↓	↓	↓	↓	↑

3. A 6-year-old boy is brought to the pediatrician because of abrupt onset of malaise, fever, and nausea. On examination, the child has mild hypertension and periorbital edema, and urinalysis is positive for protein. He recovered uneventfully from a sore throat two weeks ago. Which of the following is most likely to be found in a kidney biopsy at this time?

A. Diffuse capillary wall thickening.
B. Focal and segmental sclerosis and hyalinosis.
C. Granular IgG and C3 in the glomerular basement membrane.
D. Hyaline change in glomeruli.
E. Linear IgG and C3 deposits with fibrin in crescents.

4. A 45-year-old female with type 1 diabetes since childhood requires a kidney allograft. Her peripheral blood lymphocytes are mixed with the irradiated lymphocytes of five potential donors. Tritiated thymidine is added to the cultures and the counts per minute of radioactivity after 24 hours are measured. The results are shown in the following table:

Choice	Irradiated Cells	Responder Cells	Counts per Minute
	Recipient	Recipient	322
A.	Donor 1	Recipient	6,517
B.	Donor 2	Recipient	8,066
C.	Donor 3	Recipient	419
D.	Donor 4	Recipient	5,376
E.	Donor 5	Recipient	19,333

Which of the volunteer donors is the best choice?

A. Donor 1
B. Donor 2
C. Donor 3
D. Donor 4
E. Donor 5

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Review Questions Chapters 11–13

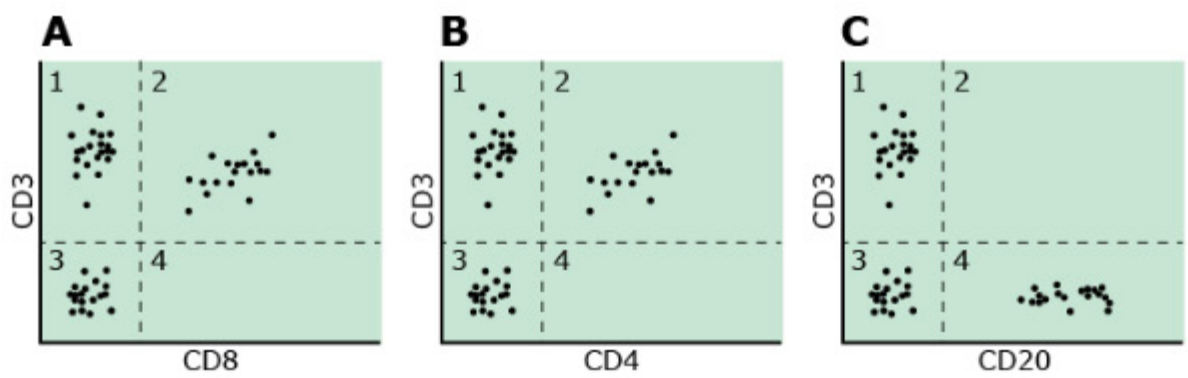
5. A 49-year-old man comes to the physician complaining of rash and diarrhea of three days' duration. He underwent bone marrow transplantation for acute myelogenous leukemia 40 days ago. Physical examination shows an erythematous maculopapular rash and jaundice. Serum studies show a total bilirubin concentration of 2.2 mg/dL and AST activity of 30 U/L. Which of the following is the most likely cause of this patient's condition?

A. Antibody- and complement-mediated cytolysis
B. Engrafted T cells sensitized to recipient alloantigens
C. Fibrinoid necrosis of vasculature secondary to immune complexes
D. IgE and mast cells
E. Sensitized recipient T cells reacting to donor alloantigens

6. A 69-year-old man is admitted to the hospital for a painless, lower GI bleed. His hemoglobin drops from 12 to 9 in four hours. His type and screen shows antibodies to B and Rh. What type of blood should he receive?

A. A+
B. A-
C. B+
D. B-
E. O+

7. The peripheral blood leukocytes of a healthy donor were stained with fluorescent-labeled monoclonal antibodies to CD3, CD4, CD8, and CD20. They were then processed through a fluorescence-activated cell sorter. In which quadrant of which graph would the sensitized cells responsible for the tuberculin test response be found?



A. Graph A quadrant 1
B. Graph A quadrant 2
C. Graph A quadrant 3
D. Graph A quadrant 4
E. Graph B quadrant 1
F. Graph B quadrant 2
G. Graph B quadrant 3
H. Graph B quadrant 4
I. Graph C quadrant 1
J. Graph C quadrant 2
K. Graph C quadrant 3
L. Graph C quadrant 4

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Chapters 11–13 Review Questions

8. A multiparous 33-year-old Rh-negative woman seeks the advice of her physician regarding the risks of having another child. She has received standard anti-Rh therapy with each of her pregnancies. Which of the following tests is best to establish her current antibody status?

A. Direct Coombs test
B. Enzyme-linked immunoassay
C. Flow cytometry
D. Indirect Coombs test
E. Radioimmunoassay

9. An outbreak of atypical pneumonia in visitors to a regional hospital is investigated by local health care officials. Cultures from a water wall in the hospital lobby are positive for *Legionella pneumophila*. Tests of patient sputum are ordered to prove the diagnosis. Which of the following procedures would allow the visualization of the causative organism in sputum samples?

A. Coombs test
B. Direct fluorescent antibody test
C. Enzyme-linked immunoassay
D. Indirect fluorescent antibody test
E. Western blot

10. A 21-year-old female goes to her college clinic. She admits concerns about unsafe sexual practices and requests standard screening for HIV. When this test is returned with positive results, the physician requests a second blood sample for a confirmatory test. Which of the following tests will the laboratory perform?

A. Enzyme-linked immunoassay
B. Flow cytometry
C. Radioallergosorbent test
D. Radial immunodiffusion
E. Western blot

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Review Answers Chapters 11–13

1. The correct answer is D. This is a case of poison ivy or poison oak that is a hapten-carrier response to the oil in the plant leaves. It is a type IV hypersensitivity mediated by sensitized Th1 cells and the cell-mediated effectors they stimulate.

2. The correct answer is C. The patient is suffering from rheumatoid arthritis, which is a type IV hypersensitivity mediated by Th1 and Th17 cells. It is diagnosed by the finding of rheumatoid factor in the serum that is IgM against the Fc region of the patient's own IgG. Although damage within the vasculature can be mediated by these immune complexes, the damage to the joints is due to cell-mediated immunity.

3. The correct answer is C. This child is suffering from post-streptococcal glomerulonephritis. This is a type III immune-complex hypersensitivity, so deposition of complexes of antigen and antibody with complement forms in an irregular pattern anywhere there are small diameter blood vessels.

4. The correct answer is C. The assay described is a one-way mixed lymphocyte response. Because radioactivity in this culture is reflective of DNA synthesis and cellular cloning, the donor/recipient combination with the lowest counts of radioactivity is the best match at the MHC class 2 loci.

5. The correct answer is B This patient is experiencing a graft versus host reaction, in which sensitized T cells in the bone marrow inoculum multiply and attempt to kill the MHC-mismatched cells of the recipient.

6. The correct answer is B. The patient who has antibodies to B alloantigens and Rh alloantigens is by definition an A, Rh- individual. The genotype could be AA or AO, Rh-/Rh-, so transfusion with either universal donor blood (O, Rh-) or A, Rh- blood would be safe.

7. The correct answer is F. The sensitized cells that control the tuberculin test result are Th1 cells. All Th cells have the same membrane markers, CD3 and CD4. The cells expressing the highest levels of both of these markers are found in the upper right quadrant of graph B.

8. The correct answer is D. To determine whether a multiparous woman has antibodies to Rh factor in her blood that would endanger a pregnancy, the indirect Coombs test is performed.

9. The correct answer is B. The direct fluorescent antibody test is the only one in the list that identifies antigen in tissue samples. All of the other tests detect antibodies against a particular antigen.

10. The correct answer is E. The confirmatory test for HIV infection is the Western blot. It is a test for antibodies against viral antigens, but unlike the EIA, which suffers from too much sensitivity, this test is insensitive. Thus, finding positive results on both tests has a very high diagnostic value.

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Clinical Case 1

Immunodeficiency Syndromes Resulting From Failed VDJ Rearrangement

History

A 2-week-old infant is brought to the pediatrician by her mother. The child weighed 6 pounds at birth and has since lost 3 ounces. Her mother complains that she has had only loose stools since she was released from the hospital.

Physical Findings

- Erythroderma with pachydermia and desquamation
- Alopecia
- Hepatosplenomegaly

Laboratory Results

- Leukocytosis
- Eosinophilia
- Elevated IgE levels

Diagnosis: Omenn syndrome

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▲ **Figure C–1** Omenn Syndrome

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Clinical Case 1

(continued)

Discussion

Omenn syndrome is a genetic disorder with autosomal recessive inheritance. It manifests as a severe combined immunodeficiency (SCID) because the mutations involve the *RAG1* and *RAG2* genes, which are essential for VDJ recombination in lymphocytes. Because lymphocytes without antigen receptors are nonfunctional, the condition is associated with virtual absence of B cells. T cell counts are elevated but they are autoreactive, perhaps because of the failure of thymic education in the absence of a functional TCR. T cell activity is the source of the red rash, desquamation, and generalized autoimmune destruction of highly mitotic cells. This makes the syndrome resemble graft versus host disease in that T cells in individuals with Omenn syndrome recognize and attack self cells. If not treated with bone marrow transplantation, the syndrome will generally prove fatal within the first two to six months of life.

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Clinical Case 2

History

A 4-year-old child is referred to a specialist because of recurrent necrotic lesions on the legs and arms. His previous history reveals that he had delayed umbilical cord separation and has had a WBC count greater than 2 x 10^4/μL on multiple occasions in the absence of evidence of infection.

Physical Findings

- Fever
- Gingivostomatitis
- Serosanguineous fluid oozes from necrotic lesions

Laboratory Results

Flow cytometry shows an absence of CD18 on myeloid cells.

Diagnosis: Leukocyte adhesion deficiency

Discussion

Leukocyte adhesion deficiency type I (LAD 1) results from failure to produce CD18, which is the common β2 subunit of the β2 integrins (LFA-1 family). β2 integrins are involved in leukocyte diapedesis, but also serve as receptors for C3b to promote opsonization and phagocytosis. Binding of β2 integrins to their ICAM ligands induces intracellular signaling that is important for a host of other cellular functions including cytokine production, cytotoxicity, apoptosis, and proliferation. Microbial infections can be handled temporarily with antibiotics in these patients, but the long-term solution is bone marrow transplantation.

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Clinical Case 3

History

A 4-year-old boy is brought to the pediatrician because of severe recurrent subcutaneous abscesses. His mother denies any history of eczema or typical childhood illnesses such as chickenpox. The child has had all of his immunizations.

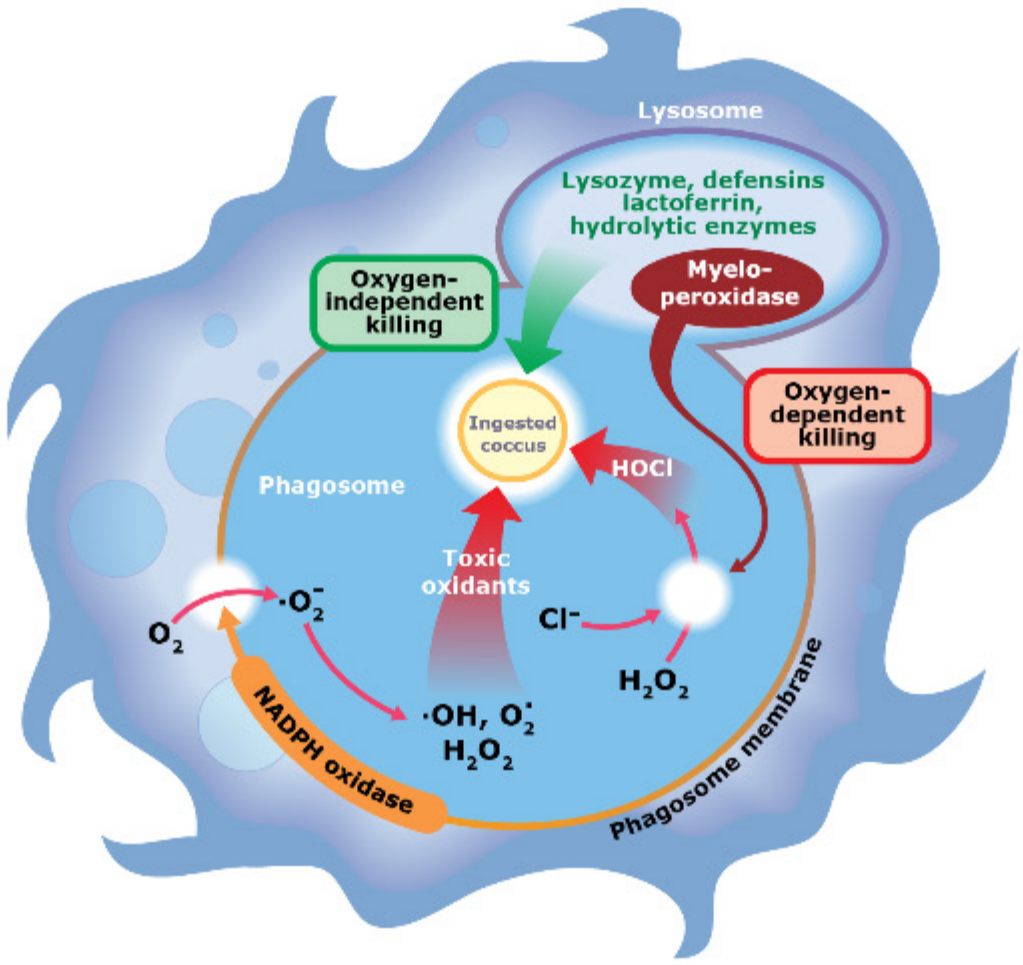
Physical Findings

With the exception of abscesses, no abnormalities are found.

Laboratory Results

- Peripheral blood leukocytosis
- Microcytic, hypochromic anemia
- Culture of pus grows catalase-positive, gram-positive cocci
- Elevated levels of IgG, IgM, and IgA
- B and T lymphocyte counts within normal limits
- Nitroblue tetrazolium dye test is negative

Diagnosis: Chronic granulomatous disease



▲ **Figure C–3A** Killing Within the Phagocyte

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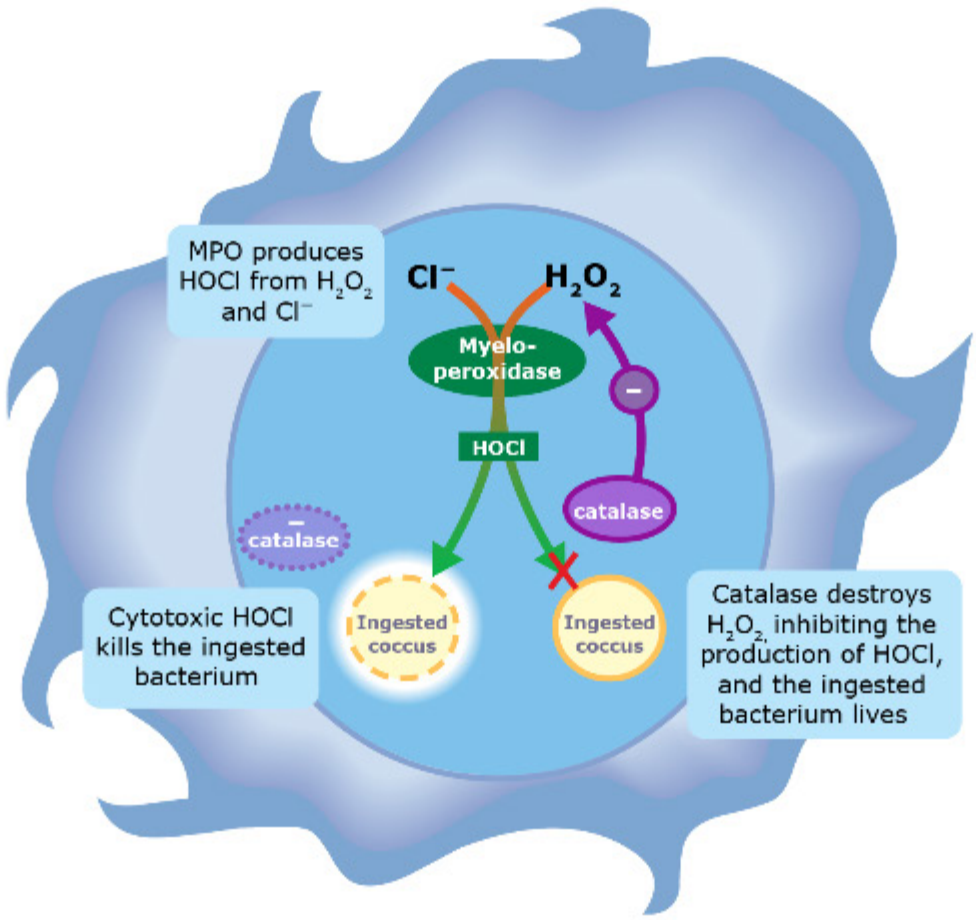
Clinical Case 3

(continued)

Discussion

Chronic granulomatous disease (CGD) is a primary immunodeficiency disease which results from an inability to produce any one of several subunits of the enzyme *NADPH oxidase*. Because of this, the patient is genetically unable to produce the oxygen radicals that are a key component of the phagocyte's ability for intracellular killing of microbes. In many cases, however, the hydrogen peroxide that is produced as a metabolic by-product of aerobic respiration by microbes can be used against them, as the substrate for the second oxygen-dependent killing mechanism involving *myeloperoxidase*. The problem with recurrent infections in these patients occurs then, when they are infected with *catalase-positive* organisms that destroy their own metabolic product (hydrogen peroxide). In such cases, both of the oxygen-dependent killing mechanisms are inactive and, left alone, the remaining contents of the lysosomes are never enough to accomplish microbial killing.



▲ **Figure C–3B** Intracellular Killing in CGD

The diagnosis of CGD is usually accomplished using the *nitroblue tetrazolium (NBT)* dye reduction test.

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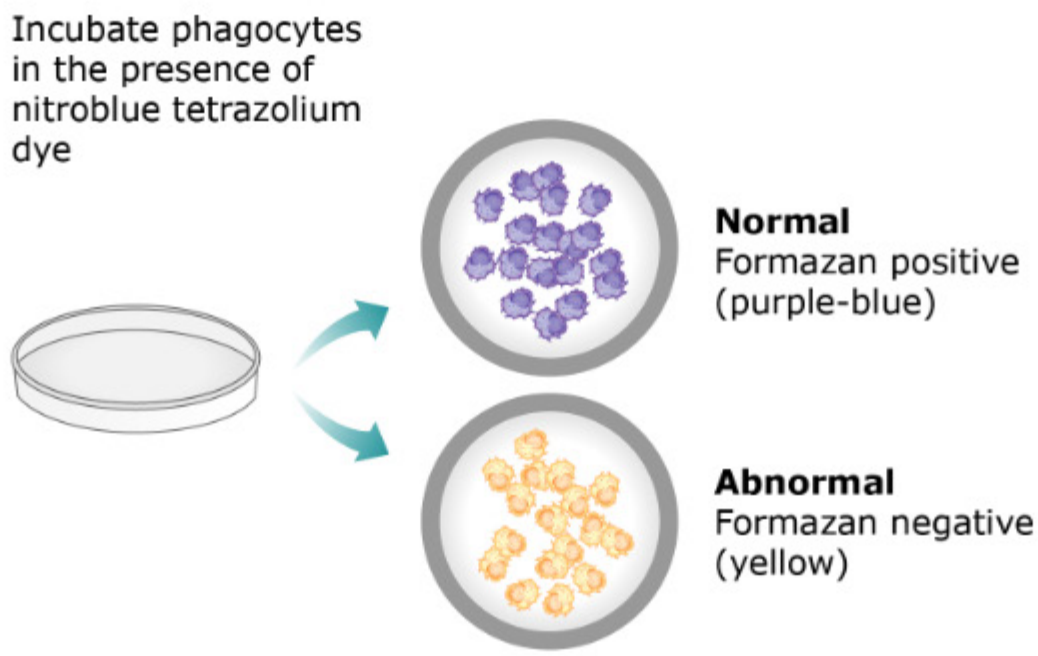
Clinical Case 3

(continued)



▲ **Figure C–3C** Nitroblue Tetrazolium Reduction

Therapy of CGD involves lifelong, aggressive antimicrobial prophylaxis along with subcutaneous interferon-gamma.

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Clinical Case 4

History

A 12-month-old male infant is referred to a specialist for failure to thrive. He has developed numerous upper and lower respiratory tract infections and protracted diarrhea.

Physical Findings

Height and weight are at the 30th percentile for age.

Laboratory Results

- Neutropenia
- Thrombocytopenia
- Anemia
- Mitogen proliferation is normal
- Low serum concentrations of IgG and IgA and elevated levels of IgM
- Flow cytometry for CD40L on T cells is negative

Diagnosis: X-linked hyper-IgM syndrome

Discussion

Hyper-IgM syndrome is a family of disorders affecting the ability of B lymphocytes to isotype switch. The most common form, X-linked hyper-IgM syndrome, results from failure of expression of CD40L on Th cells. As a result, these patients suffer deficiencies of IgG, IgA, and IgE, and extreme elevation of levels of IgM (sometimes reaching 2,000 mg/dL when normal is 45-250 mg/dL). Large numbers of IgM-producing plasma cells will be found in the bloodstream as well as autoantibodies to erythrocytes, neutrophils, and platelets. Patients will suffer recurrent gastrointestinal and pulmonary infections because IgA is the most important protector of the mucosal surfaces, and *Pneumocystis* pneumonia is common. B cell responses to T cell independent antigens will be normal.

Clinical Consequences

Without bone marrow transplantation, this disease is often fatal by age 25. Recombinant granulocyte-colony stimulating factor (G-CSF) to combat chronic neutropenia, antimicrobial therapy for infections, immunosuppressants for autoimmune disorders, and intravenous immunoglobulin are all used as required.

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Clinical Case 5

History

A 42-year-old male sees a urologist, complaining that he has occasional cola-colored urine some mornings. He says the incidents have been increasing in frequency over the past several years, as has his sensation of chronic fatigue.

Physical Findings

- Skin pallor
- Fever 39°C
- Gingival bleeding
- Skin ecchymoses

Laboratory Results

- Urinalysis: Hemoglobinuria and hemosiderinuria
- Blood: Hemoglobinemia and haptoglobinemia, increased lactate dehydrogenase, reticulocyte count, and bilirubin
- Direct antiglobulin test was negative
- Acidified serum lysis test was positive
- Flow cytometry for CD55 was negative

Diagnosis: Paroxysmal nocturnal hemoglobinuria

Discussion

This disease results from an acquired defect in myeloid stem cells. When platelets, leukocytes, and erythrocytes lose the ability to express *glycosylphosphatidylinositol (GPI)* on their membranes, they lose the ability to express *decay accelerating factor (DAF; C3 convertase inhibitor; CD55)* and *membrane inhibitor of reactive lysis (MIRL; C5 convertase inhibitor; CD59)*. These two membrane molecules are essential protection to prevent the accidental binding of complement components and avoid membrane lysis. Because these normal blood cells have no protection from complement-mediated lysis, at night, when shallow breathing can cause a respiratory acidosis, complement activation will occur and produce the paroxysmal micturition of hemoglobin.

Clinical Consequences

These patients typically die within 10 years of diagnosis due to thrombosis. The paroxysmal release of platelet contents into the blood due to complement lysis causes hepatic, portal, and cerebral thromboses. In the absence of bone marrow transplantation, iron deficiency anemia will persist, and 10% of patients will develop acute myelogenous leukemia.

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Clinical Case 6

History

A 4-year-old boy is referred to a specialist for evaluation of persistent nonmalignant lymphadenopathy and splenomegaly of 9 months' duration. More recently, the child has developed idiopathic thrombocytopenic purpura.

Physical Findings

- Lymphadenopathy of cervical, axillary, and femoral lymph node chains
- Petechiae
- Pallor
- Icterus

Laboratory Results

Elevated double-negative (TCR+, CD3+, CD4-, CD8-) T lymphocytes and relative lymphocytosis

Diagnosis: Autoimmune lymphoproliferative syndrome (Canale-Smith syndrome)

Discussion

Mutations of the FAS gene have been identified as the cause of 74% of all cases of autoimmune lymphoproliferative syndrome, although other causes include genetic defects in the FasL gene, the caspase 10 gene, and the caspase 8 gene. These disorders result in the failure of normal apoptosis that should follow lymphocyte activation. This causes inappropriate persistence and accumulation of autoreactive lymphocytes that are double-negative, and increased risk of lymphoma. Some studies suggest that these are oligoclonal Tc cells that have subsequently lost CD8 expression.

Clinical Consequences

Most patients will have a normal life span, but life-threatening cytopenias may be chronic and refractory. Splenectomy is often necessary, with the associated risk of asplenic sepsis.

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Clinical Case 7

History

A 10-year-old boy is referred to a specialist because of chronic sinusitis and postnasal drip. Since the age of 6 months, he has been plagued with otitis media, bronchitis, and bacterial pneumonia.

Physical Findings

- Brown nodular plaques on extremities and face
- Symmetrical purpura on extremities
- Nasal discharge, polyps, septum ulcers
- Chest CT scan reveals bronchiectasis

Laboratory Results

Fluorescence-activated cell sorter (FACS) analysis of peripheral blood demonstrates an absence of MHC class 1 expression.

Diagnosis: MHC class 1 deficiency (TAP deficiency syndrome, bare lymphocyte syndrome type 1)

Discussion

MHC class 1 deficiency can lead to a diverse disease spectrum, but in some patients defects in *TAP1* or *TAP2* genes have involved the generation of a premature STOP codon. In the absence of an ability to generate $\alpha\beta$ CD8+ T cells, there is an expansion of NK and $\gamma\delta$ T cells which may be involved in the pathogenesis of the granulomatous skin lesions. These cells also may account for the absence of severe viral infections.

Clinical Consequences

Patients often die of chronic lung damage and bronchiectasis due to the recurrent bacterial infections. For this reason, therapy is centered on early diagnosis and aggressive treatment of respiratory infections.

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Clinical Case 8

History

A 6-month-old female is referred to an immune specialist following a diagnosis of *Pneumocystis* pneumonia. She was treated successfully with pentamidine, but a severe combined immunodeficiency was suspected and immunological studies were undertaken.

Physical Findings

- No abnormalities found.

Laboratory Results

- Complete blood count: 20,000 WBC/μL; 82% neutrophils, 10% lymphocytes, 6% monocytes, 2% eosinophils
- Immunoglobulin analysis: IgG 96 mg/dL, IgA 6 mg/dL, IgM 30 mg/dL
- Absent in vitro response to tetanus toxoid despite normal vaccination history
- T cells responsive to allogeneic B cells in culture
- Lymphocytes treated with fluorescent-labeled antibodies to HLA-DQ and HLA-DR did not fluoresce

Diagnosis: MHC class 2 deficiency (bare lymphocyte syndrome type 2)

Discussion

MHC class 2 deficiency is inherited as an autosomal recessive trait. Health problems begin in infancy. These patients are deficient in CD4 Th cells and have moderate to severe hypogammaglobinemia. In contrast to bare lymphocyte syndrome type 1 (MHC class 1 deficiency), these patients have normal numbers of CD8+ Tc cells. The deficiency results from defects in the transcription factors required to regulate MHC class 2 molecule expression.

Clinical Consequences

Therapy for patients with bare lymphocyte syndrome involves bone marrow transplantation. Because the patient's cells have no MHC class 2 molecules, there will be no graft versus host disease, and engraftment is normally curative.

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Table A–1.1 Cytokines

Cytokine	Secreted By	Target Cell/Tissue	Activity
Interleukin (IL)-1	Monocytes, macrophages, B cells, dendritic cells, endothelial cells, others	Th cells	Co-stimulates activation
		B cells	Promotes maturation and clonal expansion
		NK cells	Enhances activity
		Endothelial cells	Increases expression of ICAMs
		Macrophages and neutrophils	Chemotactically attracts
		Hepatocytes	Induces synthesis of acute-phase proteins
		Hypothalamus	Induces fever
IL-2	T cells	Antigen-primed Th and Tc, NK cells, B cells	Induces proliferation, enhances activity
IL-3	T cells	Hematopoietic cells (myeloid)	Supports growth and differentiation
IL-4	Th2 cells	T cells	Th2 differentiation, proliferation
		Activated B cells	Isotype switch to IgE
IL-5	Th2 cells and mast cells	Activated B cells	Stimulates proliferation, isotype switch to IgA
		Bone marrow cells	Induces eosinophil differentiation
		Eosinophils	Activation, stimulates proliferation
IL-6	Monocytes, macrophages, Th2 cells, bone marrow stromal cells	Proliferating B cells	Promotes terminal differentiation into plasma cells
		Hepatocytes	Induces synthesis of acute-phase proteins
IL-7	Bone marrow, thymic stromal cells, fibroblasts	Lymphoid stem cells	Induces differentiation into lymphoid progenitor cells
IL-8	Macrophages, endothelial cells	Neutrophils	Chemokine; induces adherence to endothelium and extravasation into tissues
IL-10	Th2 cells and Treg cells	Macrophages	Suppresses cytokine production by Th1 cells
IL-11	Bone marrow stroma	Bone marrow	Promotes megakaryocyte differentiation
IL-12	Macrophages and B cells	Th0, Th1, activated Tc	Acts synergistically with IL-2 to induce differentiation into Tc; promotes Th1 production
		NK cells	Stimulates proliferation
IL-13	Th2 cells and mast cells	B cells	Induces isotype switch to IgE, IgG1
IL-17	Th17 cells	Fibroblasts, endothelial cells, macrophages	Increases inflammation; attracts PMNs; and induces IL-6, IL-1, TGF-β, TNF-α, IL-8
IL-35	Treg	Th1, Th2, Th17	Inhibits Th1, Th2, Th17; stimulates Treg
Interferon-α (type I)	Leukocytes	Uninfected cells	Inhibits viral replication and increases MHC 1 and 2 expression

(continued)

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Table A–1.1 Cytokines (continued)

Cytokine	Secreted By	Target Cell/Tissue	Activity
Interferon-β (type I)	Fibroblasts	Uninfected cells	Inhibits viral replication and enhances MHC 1 and 2 expression
Interferon-γ (type II)	Th1, CTLs, NK cells	Macrophages	Enhances activity; therapy for CGD (chronic granulomatous disease)
		Many cell types	Increases expression of MHC 1 and 2
		Proliferating B cells	Induces class switch to IgG2a; blocks IL-4-induced class switch to IgE and IgG1
		Th2 cells	Inhibits proliferation
Transforming growth factor-β	Platelets, macrophages, lymphocytes, mast cells	Proliferating B cells	Induces class switch to IgA
Tumor necrosis factor-α	Macrophages and NK cells	Tumor cells	Has cytotoxic effect
		Inflammatory cells	Induces cytokine secretion; cancer cachexia
Tumor necrosis factor-β (lymphotoxin)	Th1 and Tc	Tumor cells	Has cytotoxic and other effects, like TNF-α
		Macrophages and neutrophils	Enhances phagocytic activity
Granulocyte colony-stimulating factor (G-CSF)	Macrophages and Th cells	Bone marrow granulocyte precursors	Induce proliferation; used clinically to counteract neutropenia following ablative chemotherapy
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Macrophages and Th cells	Bone marrow granulocyte and macrophage precursors	Induces proliferation; used clinically to counteract neutropenia following ablative chemotherapy

Table A–1.2 Cytokines Available in Recombinant Form

Cytokine	Clinical Uses
Erythropoietin	Anemias, especially those associated with renal failure
Filgrastim (G-CSF)	Stimulates granulocytes; used for bone marrow recovery
Interferon-α	Hepatitis B and C, leukemias, melanoma
Interferon-β	Multiple sclerosis
Interferon-γ	Chronic granulomatous disease → stimulates TNF
Oprelvekin (IL-11)	Stimulates platelet production
Sargramostim (GM-CSF)	Stimulates granulocytes and macrophages; used for marrow recovery

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Key

ADCC:	antibody-dependent cell-mediated cytotoxicity	MHC:	major histocompatibility complex
APC:	antigen-presenting cell	NK:	natural killer
CALLA:	common acute lymphoblastic leukemia antigen	Tc:	cytotoxic T cell
CD:	cluster of differentiation	TCR:	T cell receptor
LFA:	leukocyte function–associated antigen	Th:	T helper
LPS:	lipopolysaccharide		

Table A–2.1 CD Markers

CD Designation	Cellular Expression	Known Functions
CD2 (LFA-2)	T cells, thymocytes, NK cells	Adhesion molecule; binds CD58
CD3	T cells and thymocytes	Signal transduction by the TCR
CD4	Th cells, thymocytes, monocytes, macrophages	Co-receptor for TCR-MHC 2 interaction; receptor for HIV
CD8	Tc, some thymocytes	Co-receptor for MHC class 1–restricted T cells
CD10 (CALLA)	Immature B cells and lymphoid progenitors	Metalloproteinase, B cell development
CD14 (LPS receptor)	Monocytes, macrophages, granulocytes, dendritic cells	Binds LPS (endotoxin)
CD16 (Fc receptor)	NK cells, macrophages, neutrophils	Opsonization; ADCC
CD18	Leukocytes	β chain of β2 integrins; cell adhesion molecule (missing in leukocyte adhesion deficiency)
CD19	B cells	Co-receptor with CD21 for B cell activation (signal transduction)
CD20	Most or all B cells	Unknown role in B cell activation
CD21 (CR2, C3d receptor)	Mature B cells	Receptor for complement fragment C3d; forms co-receptor complex with CD19; Epstein-Barr virus receptor
CD25	Activated Th cells and Treg cells	Alpha chain of IL-2 receptor
CD28	T cells	T cell receptor for costimulatory molecule B7
CD34	Precursors of hematopoietic cells and endothelial cells in HEV	Cell-cell adhesion; binds L-selectin
CD40	B cells, macrophages, dendritic cells, endothelial cells	Binds CD40L; role in T cell dependent B cell, macrophage, dendritic cell, and endothelial cell activation
CD45 (leukocyte common antigen)	Hematopoietic cells	TCR/BCR receptor-mediated signaling
CD54 (ICAM-1)	T and B cells, monocytes endothelial cells	Adhesion; ligand for β2integrins; receptor for rhinovirus
CD55 (decay-accelerating factor, DAF)	Ubiquitous	Binds C3b and C4b; regulates complement activation
CD56	NK cells	Not known
CD58 (LFA-3)	Ubiquitous	Binds CD2; adhesion
CD59 (membrane inhibitor of reactive lysis; MIRL)	Ubiquitous	Binds C9; inhibits complement membrane attack complex
CD80 (B7)	Dendritic cells, activated B cells, macrophages	Ligand for CD28 and CD152 (CTLA-4)
CD152 (CTLA-4)	Activated T cells	Binds CD80 (B7) on APC, inhibitory signal to T cell

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Table A–3.1 Cell Adhesion Molecules

Family	Function	Name	Tissue Distribution	Ligand
Selectins	Bind carbohydrates; *initial binding* leukocyte-endothelia	L-selectin	Leukocytes	Addressins
		P-selectin	Endothelium and platelets	Addressins
		E-selectin	Activated endothelium	Addressins
Mucin-like vascular *addressins*	Bind to L-selectin and initiate leukocyte endothelial interaction	CD34	Endothelial venules	L-selectin
		Gly-Cam-1	High endothelial venules	L-selectin
		MAdCAM-1	Mucosal lymphoid tissue venules	L-selectin
Integrins	Bind to cell-adhesion molecules and extracellular matrix; *strong adhesion*	LFA-1	Monocytes, T cells, macrophages, neutrophils, dendritic cells	ICAMs
		CR3	Neutrophils, monocytes, macrophages	ICAM-1, iC3b, fibrinogen
		CR4	Dendritic cells, macrophages, neutrophils	iC3b
Immunoglobulin superfamily cellular adhesion molecules (ICAMs)	Various roles in cell adhesion; ligand for integrins	CD2	T cells	LFA-3
		ICAM-1	Activated vessels, lymphocytes, dendritic cells	LFA-1, CR3
		ICAM-2	Resting vessels, dendritic cells	LFA-1
		ICAM-3	Lymphocytes	LFA-1
		LFA-3	Lymphocytes, antigen-presenting cells	CD2
		VCAM-1	Activated endothelium	VLA-4

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Table A–4.1 The Immune Response in Infection

Category	Pathogen	Protective Mechanism	Evasive Mechanism	Immune Pathology
Extracellular bacteria	All	Ab or C enhance phagocytosis or block toxin binding		
Gram-positive, extracellular bacteria	*Streptococcus pyogenes*	Opsonization with Ab and C3b	Hyaluronic acid capsule is nonimmunogenic	Exotoxins act as superantigens, nonsuppurative sequelae: types II and III hypersensitivities
Catalase-positive bacteria	All	Opsonization with Ab and C3b	Catalase destroys H_2O_2 substrate for myeloperoxidase	Serious in CGD patients
	Staphylococcus aureus	Opsonization with Ab and C3b	Protein A binds Fc of IgG and inhibits opsonization	Exotoxins act as superantigens
Encapsulated bacteria	All	Opsonization with Ab and C; spleen is critical	Resist phagocytosis	Abscess formation
IgA protease producers	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis,* and *Neisseria gonorrhoeae*	Opsonization with Ab and C; spleen is critical	Destroy IgA	Abscess formation
Coagulase-positive bacteria	*Staphylococcus aureus* and *Yersinia pestis*	Opsonization with Ab and C; spleen is critical	Inhibit phagocytosis	Abscess formation
Gram-negative extracellular bacteria	All	Ab or C enhance phagocytosis or block toxin binding		LPS activates macrophages → IL-1 and TNF-α
	Neisseria gonorrhoeae	MAC lyses	Antigenic variation of pill and outer membrane proteins	
	Neisseria meningitidis	MAC lyses	Type B sialic acid capsule is nonimmunogenic	
	Pseudomonas	Ab or C enhance phagocytosis or block toxin binding	Inactivates C3a and C5a	
	Borrelia burgdorferi			Immune complexes cause rash, arthritis, neurologic symptoms
	Treponema pallidum			Indigestible, chronic organism promotes granuloma formation (gummas)
Intracellular bacteria	All	Th1 cells activate NK, macrophages, and CTLs		
	Mycobacterium tuberculosis	Th1 produces IFN-γ to make angry macrophages	Sulfatides inhibit phagolysosome formation	Granuloma formation is CMI-mediated
	Mycobacterium leprae	Th1 stimulation is protective in tuberculoid form	Th2 stimulation results in lepromatous form	Nerve damage in tuberculoid form is DTH-mediated

(continued)

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Table A–4.1 The Immune Response In Infection (continued)

Category	Pathogen	Protective Mechanism	Evasive Mechanism	Immune Pathology
Intracellular bacteria (continued)	*Listeria monocytogenes*	DTH and Tc	Hemolysin disrupts phagosome membrane, allows escape into cytoplasm	
	Chlamydia trachomatis	DTH and Tc		Scarring of fallopian tubes is DTH-mediated
Viruses	Naked capsid (all)	Antibody blocks receptor binding; CMI destroys infected cells		
	Rhinovirus	See above	Antigenic drift	
	Adenovirus	See above	Decreases MHC 1 expression	
	Syncytial viruses (herpesviridae, paramyxoviridae, HIV)	CMI is essential		
	Enveloped (all)	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK		
	Hepatitis C	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Blocks IFN-α and -β	
	Hepatitis B	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK		Immune complexes cause vasculitis
	All herpesviridae	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Nuclear membrane envelope is nonimmunogenic	
	Herpes simplex 1 and 2	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Block TAP function (inhibits MHC 1 expression), viral glycoprotein ↓ C activation	
	Cytomegalovirus	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Generalized immunosuppression; ↓ MHC 1 and 2 expression; produces chemokine receptor and MHC 1 homologues	
	Epstein-Barr virus	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Generalized immunosuppression; produces molecule homologous to IL-10 (shuts down Th1)	Activates B cells, causes production of heterophile Abs
	Paramyxoviruses	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Generalized immunosuppression	

(continued)

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Table A–4.1 The Immune Response in Infection (continued)

Category	Pathogen	Protective Mechanism	Evasive Mechanism	Immune Pathology
Viruses (continued)	Human immunodeficiency virus	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Infects and kills $CD4^+$ cells, antigenic drift	
	Rubeola	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	↓ MHC 2 expression	
	Influenza	Antibody blocks receptor binding; C lyses envelope; Ab and C enhance phagocytosis; Th1 cells stimulate Tc and NK	Antigenic shift and drift	
Prion	CJD, kuru, etc.	No immune response	None	None
Fungi	Most	Phagocytosis by PMNs and macrophages; Abs not protective		Calcifying lesions due to indigestibility of cell-wall carbohydrates
	Cryptococcus neoformans	As above	Inhibits Th1; stimulates Th2, capsule protects against phagocytosis	
	Histoplasma capsulatum	Th1 cell stimulates macrophages and Tc		Granulomas and calcifications
Extracellular protozoa	All	Abs to surface molecules plus C cause lysis or opsonize		
	Trypanosoma brucei rhodesiense and *gambiense*	Abs to surface molecules plus C cause lysis or opsonize	Antigenic variation of variable surface glycoprotein	
	Entamoeba histolytica	Abs to surface molecules plus C cause lysis or opsonize	Antigen shedding	
Intracellular protozoa	All	Th1 cells stimulate macrophages and Tc		
	Plasmodium spp.	Antibodies plus C; spleen is critical	Maturational stages change antigens; antigenic variation	
	Trypanosoma cruzi	Amastigotes killed by CMI; trypomastigotes (extracellular) killed by Ab and C		
	Leishmania spp.	Th1 cells stimulate macrophages, Tc		
Helminth parasites	All	ADCC-mediated by eosinophils and macrophages		
	Filarial nematodes	ADCC-mediated by eosinophils and macrophages	Immunosuppression secondary to lymphatic obstruction	
	Schistosoma spp.	ADCC-mediated by eosinophils and macrophages	Adult envelops itself in host self-glycoproteins (ABO and MHC antigens)	Granulomas in liver due to DTH response to egg antigens

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Microbiology

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1 Comparative Anatomy and Physiology of Infectious Agents

▼ **Table 1–1.0** Infectious Agents

Characteristics	Prions	Viruses	Bacteria	Fungi	Parasites
Diameter	Molecular	0.02–0.3 microns	0.3–2 microns	3–10 microns	15–25 microns
Cell Type	Acellular	Acellular	Prokaryotic cells	Eukaryotic cells	
		Use host organelles; obligate intracellular parasites	No membrane-bound organelles	Mitochondria and other membrane-bound organelles	
	No DNA or RNA; infectious protein	DNA or RNA	DNA and RNA	DNA and RNA	
	Deposits extracellularly	Replicates in host cells	DNA replicates continuously	G and S phase (cell cycle)	
			Mono- and poly-cistronic mRNA	Monocistronic mRNA	
			Exons, no introns	Introns and exons	
	No ribosomes	No ribosomes	70S ribosomes (30S and 50S) Tetracycline inhibits	80S ribosomes (40S and 60S)	
Replication	Alteration of configuration of normal cellular proteins	Make and assemble viral components	Binary fission, asexual	Cytokinesis with mitosis	
Cellular Membrane	None	Some are enveloped, but without membrane function	No sterols except *Mycoplasma*, which has cholesterol	Ergosterol is major sterol; synthesis targeted by nystatin and imidazoles	Sterols such as cholesterol
Cell Wall	None	No cell wall	Peptidoglycan; synthesis targeted by penicillin and cephalosporins	Complex carbohydrate cell wall (chitin, glucan, mannan)	No cell wall

USMLE® Key Concepts

For Step 1, you must be able to:

- Identify the basic anatomy and physiology of the major microbial groups.
- List the important normal flora and explain how they impact diagnosis.
- Describe the major mechanisms of pathogenesis for each microbial group.

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2 Normal Flora

▼**Table 1–2.0** Normal Flora

Location	Important Organisms	Less Important Organisms
Skin	*Staphylococcus epidermidis*	*Staphylococcus aureus, Corynebacterium* (diphtheroids), various streptococci, anaerobes, yeasts
Nose	*Staphylococcus aureus*	*S. epidermidis, Corynebacterium* (diphtheroids), various streptococci
Oropharynx	*Viridans* streptococci; e.g., *Streptococcus mutans*	Various streptococci, nonpathogenic *Neisseria* spp., nontypeable *Haemophilus influenzae, Candida albicans*
Gingival Crevices	Various anaerobes, e.g., *Bacteroides*, *Fusobacterium*, streptococci, *Actinomyces*	
Colon	*Bacteroides fragilis, Escherichia coli*	*Clostridium, Bifidobacterium, Eubacterium, Fusobacterium, Lactobacillus*, various anaerobic gram-negative rods, *Streptococcus faecalis*, and other streptococci
Vagina	*Lactobacillus*, group B streptococci	Various streptococci and gram-negative rods, *B. fragilis, Corynebacterium* (diphtheroids), *Veillonella, C. albicans*

Clinical Application

Carrier

A person infected with a pathogen but without overt disease.

Bacteremia

Presence of bacteria in the bloodstream without clinical signs.

Septicemia

Bacteria multiplying in bloodstream with clinical symptoms.

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3 Mechanisms of Pathogenicity

3.1 Adherence

The first step for microbes to initiate infection of host tissues is adherence. Many varieties of microbial adherence mechanisms exist.

▼ **Table 1–3.1** Microbial Adherence

Category	Microbe	Adhesin	Receptor
Bacteria	Gram negatives	Pili (fimbriae)	
	Escherichia coli	Type 1 pili	Mannose
		P and S pili	Galactose
	Vibrio cholerae (type IV)	Unknown	Fucose and Mannose
	Bordetella pertussis	Pertussis toxin, filamentous hemagglutinin	Integrin?
	Gram positives	Lipoteichoic acid	Fibronectin
	Streptococcus pyogenes	M protein	Fibrinogen
	Staphylococcus epidermidis and *Streptococcus mutans*	Biofilm	Allows adherence to slippery substances
	Chlamydia	Cell surface lectin	N-acetylglucosamine
	Mycoplasma	Protein P1	Sialic acid
Viruses	Most RNA viruses	Hemagglutinin	Sialic acid
	Human immunodeficiency virus (HIV)	Gp120	CD4 plus CCR5 or CXCR4
	Epstein-Barr virus	Envelope glycoproteins	CD21 (B lymphocytes)
	Rabies virus	Envelope glycoproteins	Acetylcholine receptor
	Rhinovirus	Capsid proteins	ICAM-1
Parasites	*Plasmodium falciparum*	PfEMP1 (*Plasmodium falciparum* erythrocyte membrane protein) Erythrocyte binding antigen	ICAM-1 Glycophorins
	P. vivax	Duffy-binding protein	Duffy antigen

Dennis Kunkel Microscopy, Inc./Visuals Unlimited, Inc.

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3.2 Evasion of Phagocytosis

Once an extracellular microbe has managed to adhere in a particular location, the first wave of the immune response mounted against it is the acute inflammatory response. This action mobilizes immune cells into the area of microbial adherence, so from the microbial perspective, evasive techniques that inactivate or interfere with this process are beneficial for survival.

3.2.1 Inhibition of Chemotaxis and Complement

- *Streptococcus pyogenes*
  - *Streptococcal chemokine protease* degrades the neutrophil chemokine, IL-8
  - *C5a peptidase* inactivates C5a anaphylatoxin and impedes neutrophil chemotaxis
- *Pseudomonas aeruginosa* inactivates C3a, C5a (anaphylatoxins)

3.2.2 Capsules

Also known as *slime layers*, or glycocalyces (singular *glycocalyx*), *capsules* are gelatinous, non-adherent secretions of many extracellular microbes that protect them from phagocytosis. These slippery surface coatings act by making it difficult for phagocytic cells to engulf the invading organism.

3.2.3 Anti-opsonins

Opsonization is the coating of a particle with IgG and/or complement component C3b to enhance the speed of phagocytosis. Microbes that can inactivate this process are at a selective advantage to be protected from rapid phagocytosis.

- *M-protein* binds serum factor H, destroying C3 convertase and preventing C3b opsonization in *Streptococcus pyogenes*.
- *Protein A* binds the Fc portion of IgG in *Staphylococcus aureus*.

3.2.4 Pili

The pili of *Neisseria gonorrhoeae* are anti-phagocytic, although this is not true of all pili.

3.3 Evasion of Acquired Immunity

The acquired immune response that develops subsequent to acute inflammation has the properties of antigenic specificity and diversity of mechanisms. Microbes that can evade specific recognition through alterations of their appearance are at a selective advantage in this way.

3.3.1 Antigenic Variation

- *Neisseria gonorrhoeae*: Pili and outer membrane proteins.
- Enterobacteriaceae: Capsular and flagellar antigens.
- Many viruses (especially HIV): High mutation rates cause *antigenic drift*.
- *Segmented viruses* (especially influenza virus): Reassort their genomes causing *antigenic shift*.
- African trypanosomes: Variant specific glycoprotein.

Memory Aid

Some **K**illers **H**ave **P**retty **N**ice **S**limy **C**apsules:

***S**treptococcus pneumoniae*
***K**lebsiella pneumoniae*
***H**aemophilus influenzae* type B
***P**seudomonas aeruginosa*
***N**eisseria meningitidis*
***S**almonella* spp.
***C**ryptococcus neoformans*

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3.3.2 Intracellular Survival

Microbes capable of survival inside host cells are difficult to kill with humoral immune responses because antibodies are not transported into cells. *Facultative intracellular* microbes have evolved mechanisms for surviving inside phagocytic cells. *Obligate intracellular* microbes require the environment inside the non-phagocytic cells of the host in order to reproduce.

- *Mycobacterium tuberculosis*: Sulfatides inhibit phagosome-lysosome fusion.
- *Listeria monocytogenes*: Escape from the phagosome into the cytoplasm before lysosomal fusion.
- Syncytial viruses (paramyxoviruses, herpesviruses, HIV): Avoid humoral immunity by moving from cell to cell using fusion of cell membranes.
- Herpesviruses, adenoviruses, rubeola: Downregulate expression of MHC molecules on infected cells, making them refractory to Tc killing.

3.3.3 IgA Proteases

IgA is the major protective immunoglobulin of the mucosal surfaces. Some bacteria can produce an IgA protease that helps them evade mucosal immunity. These include:

- *Haemophilus influenzae*
- *Streptococcus pneumoniae*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*

3.4 Penetration and Spread

Microbes, once in a tissue, must acquire their necessary nutrition from host cells and multiply for survival.

- **Type III Secretion Systems:** A toxin injection device identified in the family Enterobacteriaceae, as well as *Pseudomonas* and *Chlamydia*, delivers bacterial toxins into the host cell.
- **Invasins:** These surface proteins promote binding and penetration of non-phagocytic cells, resulting in their infection, as in *Yersinia pseudotuberculosis*.
- **Competition for Nutrition:** Many bacteria produce siderophores that allow them to chelate iron and import it into their own cells.

Destruction of the extracellular matrix helps bacteria to disseminate deeper into tissues and other areas of the body.

- **Collagenase:** Breaks peptide bonds in collagen (*Clostridium perfringens*).
- **Hyaluronidase:** Breaks down hyaluronic acid (*Streptococcus pyogenes* and *C. perfringens*).
- **Lecithinase:** Disrupts cell membrane lecithin and contributes to myonecrosis (*C. perfringens*).
- **Streptokinase:** Dissolves fibrin (*Streptococcus pyogenes*).
- **Streptodornase:** Breaks down DNA released by dead cells and reduces the viscosity of pus (*Streptococcus* spp.).

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3.5 Immunologically Mediated Injury

Active immunity against microbial invasion is rarely without cost to the host. Acute inflammatory damage includes pus and abscess formation that can resolve leaving cavitary lesions or scar tissue.

3.5.1 Acute Inflammation

- **F-met Peptides (Formyl-Methionyl Peptides):** Bacteria make their peptides with formyl and methionyl residues as their starting sequences. These are strongly chemotactic for neutrophils.
- **Peptidoglycan-Teichoic Acid Fragments:** Produced from gram-positive cells. Act as:
  - Anatomical toxins released when cells die.
  - Chemotactic for neutrophils—results in these bacteria being "pyogenic."

3.5.2 Chronic Inflammation

If the immune system fails to eliminate an infectious agent, a state of chronic inflammation can be established as the immune system continues to try to contain and/or eliminate the foreign pathogen. Often, long-term tissue damage is the result of the chronic inflammatory response.

3.5.3 Hypersensitivities

▼ **Table 1-3.5** Hypersensitivities

Hypersensitivity	Disease	Manifestation
Type 1	Allergy	Misplaced anthelmintic response
Type 2	Rheumatic fever	Antibodies against streptococcal M protein cross-react with perivascular connective tissue
Type 3	Post-streptococcal glomerulonephritis	Immune complexes of antibodies against *Streptococcus pyogenes* serotypes M12 and M14 circulate with the antigen and block small diameter blood vessels
Type 4	Tuberculosis, leprosy, Chlamydial pelvic inflammatory disease	Cell-mediated immune response against infected cells causes damage and granuloma formation

3.6 Toxins

Toxins are poisonous substances produced by living cells. They can be part of the microbial anatomy or be released by microbial secretion.

3.6.1 Anatomical Toxins

Endotoxin (Lipopolysaccharide)

- Part of outer membrane of gram-negative bacterium.
- Heat stable, cannot be converted into a toxoid.
- Active component = Lipid A, released with death of cell; exception is neisserial species, which overproduce outer membrane fragments.
- Mechanism of action: Binds to CD14 on macrophages and dendritic cells, stimulates overproduction of cytokines.

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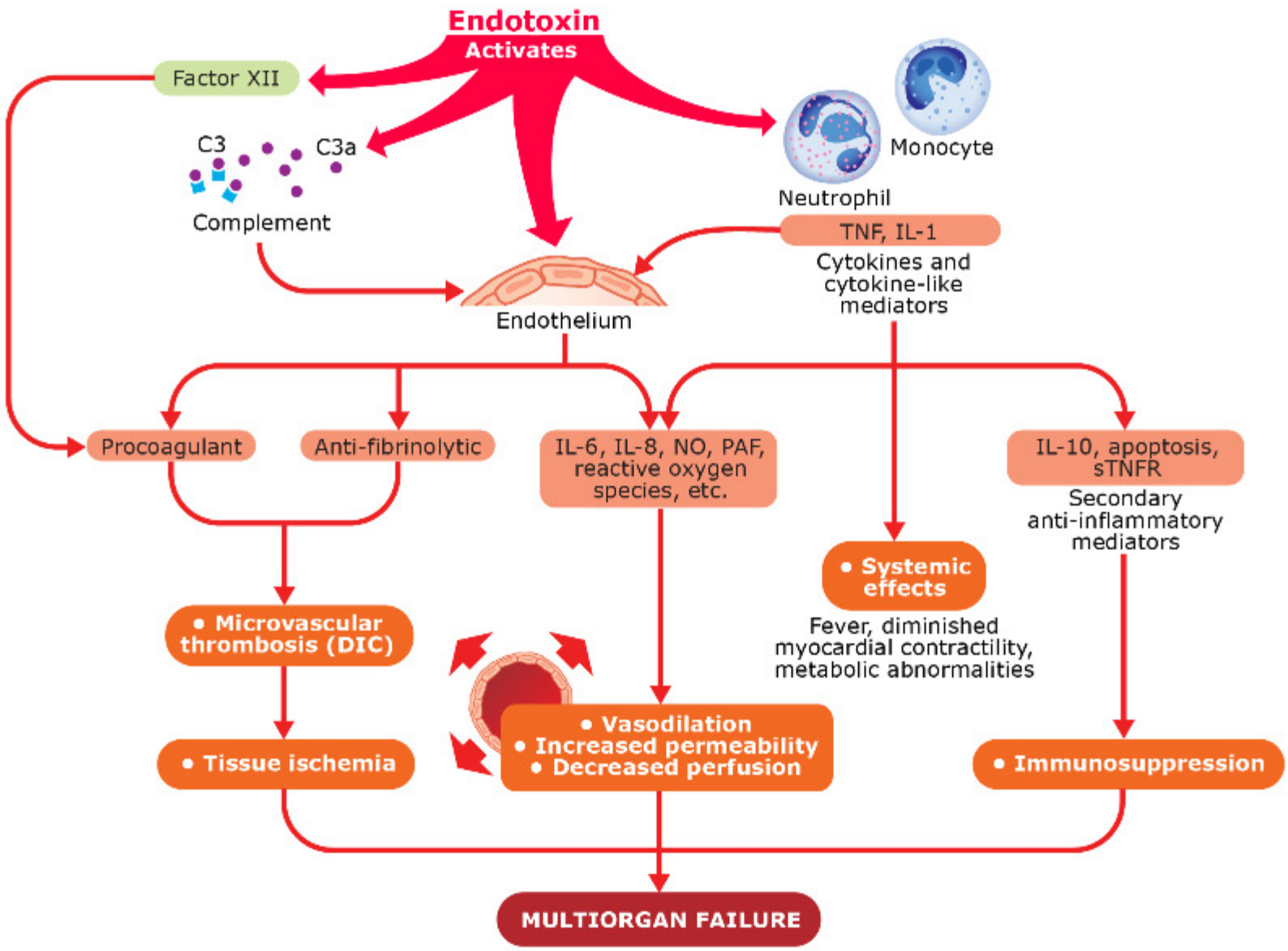
Peptidoglycan-Teichoic Acid Fragments

- Released on death of gram-positive bacteria
- Chemotactic for neutrophils

Clinical Application

Meningococcal meningitis is a medical emergency because of the extremely rapid onset of endotoxin shock caused by the overproduction of outer membrane fragments. One of the key clues toward this diagnosis is the finding of petechial hemorrhage and ecchymoses of the palate and skin from the time of onset of malaise and fever.



▲ **Figure 1-3.6** Endotoxin Action

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3.6.2 Secreted Toxins (Exotoxins)

- Protein secretions of viable cells
- Two components: A (active) and B (binding)
- Easily inactivated to make toxoid vaccines
- Classified by site of action (enterotoxins, neurotoxins, cytotoxins)
- Cytolysins: Damage membranes and lyse cells

▼Table 1-3.6 Exotoxins

Category of Activity	Organism	Toxin	Mechanism of Action	Role in Disease
Protein Synthesis Inhibitors	*C. diphtheriae*	Diphtheria toxin	ADP-ribosylates eEF-2 1° targets: heart, nerves, epithelium	Inhibits eukaryotic protein synthesis
	P. aeruginosa	Exotoxin A	ADP-ribosylates eEF-2 1° target: liver	Inhibits eukaryotic protein synthesis
	S. dysenteriae	Shiga toxin	Interferes with 60S ribosomal subunit	Inhibits eukaryotic protein synthesis
	EHEC E. coli	Verotoxin	Interferes with 60S ribosomal subunit	Inhibits eukaryotic protein synthesis
cAMP Inducers	*ETEC E. coli*	Heat labile toxin	Adenylate cyclase ADP ribosylates GTP bp	Secretion of fluids and electrolytes
	V. cholerae	Cholera toxin	Adenylate cyclase ADP ribosylates GTP bp	Profuse, watery diarrhea
	B. anthracis	Anthrax toxin	EF-edema factor LF-lethal factor PA-protective antigen	↓ Phagocytosis, causes edema and kills cells
	B. pertussis	Pertussis toxin	ADP ribosylates Gi ↑ cAMP	Edema, histamine sensitization, lymphocytosis, islet activation
Cytolysins	*C. perfringens*	α toxin	Lecithinase	Damages cell membranes, myonecrosis
	S. aureus	α toxin	Intercalates, forming pores	Cell membrane becomes leaky
Neurotoxins	*C. tetani*	Tetanus toxin	Blocks release of inhibitory transmitters glycine and GABA	Inhibits neurotransmission in inhibitory synapses, rigid paralysis
	C. botulinum	Botulinum toxin	Blocks release of acetylcholine	Inhibits cholinergic synapses, flaccid paralysis
Superantigens	*S. aureus* (gram-positive)	TSST-1	Pyrogenic, cytokine storm, ↓ liver clearance of LPS	Fever, shock, capillary leakage, cardiotoxicity
	S. pyogenes (gram-positive)	Exotoxin A, C	Similar to TSST-1	As with TSST-1

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1 The "Dogma of Life"

Ever since 1951, when Watson and Crick published their now-famous treatise stating they believed that DNA was the basic library of genetic information, we have been working with the following biological dogma: DNA is *transcribed* into RNA, which is then *translated* into protein.

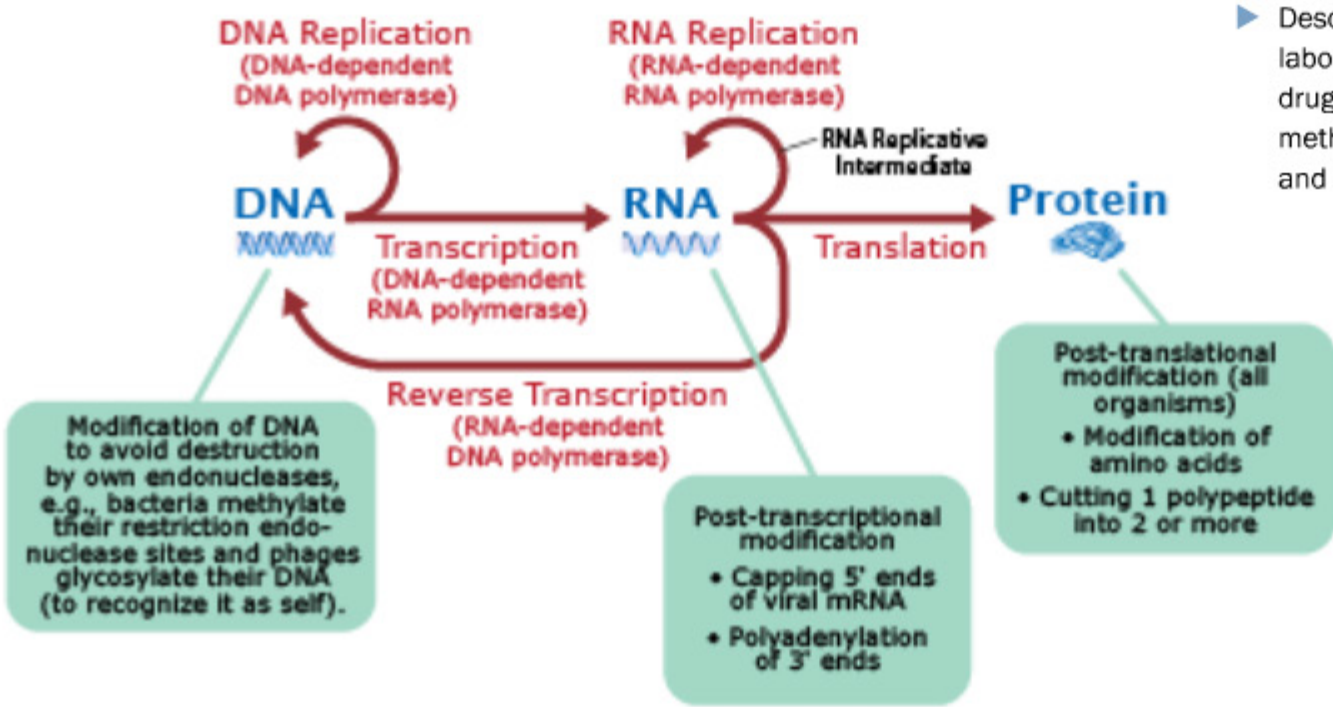
Microbes may make modifications to this process:

- RNA viruses need a way to replicate RNA, which is not done in a eukaryotic cell, so they must either produce or bring with them into the cell the necessary RNA-dependent, RNA-polymerases.
- Retroviruses and hepadnaviruses make DNA from an RNA original. This requires reverse transcription and an RNA-dependent DNA polymerase.
- Bacteria, which lack a nuclear membrane, methylate the restriction endonuclease sites on their DNA molecules to avoid accidental cleavage.
- Phages (bacterial viruses) glycosylate their restriction endonuclease sites as an early self-nonself recognition device.
- All organisms perform post-transcriptional modifications, capping the 5' ends of mRNA, polyadenylation of the 3' ends, but bacteria do not have introns, so that particular step in post-transcriptional modification does not happen in the prokaryotes.
- All organisms perform post-translational modification of proteins: modification of amino acids or cutting polypeptide chains.

USMLE® Key Concepts

For Step 1, you must be able to:

- Define the mechanisms of horizontal genetic transfer in bacteria: transformation, conjugation, and transduction.
- Explain the role of transposons in the formation of multi-drug-resistant plasmids.
- Identify the major mechanisms of bacterial drug resistance.
- Describe common laboratory techniques for drug sensitivity testing, and methods for sterilization and disinfection.



▲ **Figure 2-1.0A** Dogma of Life: Microbial Modifications

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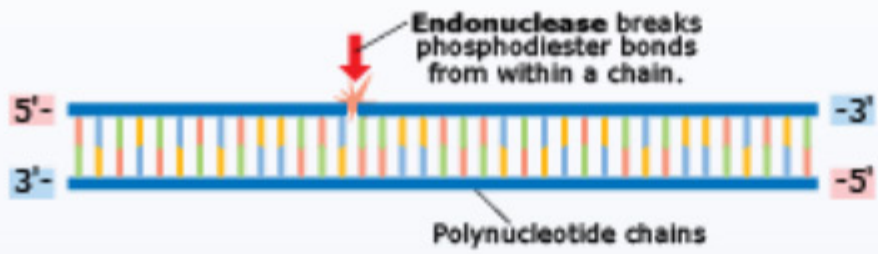
Connection to Biochemistry

Polymerases are enzymes that synthesize nucleic acid strands. They are named using the following convention:

▲ **Figure 2-1.0B** DNA and RNA Polymerases

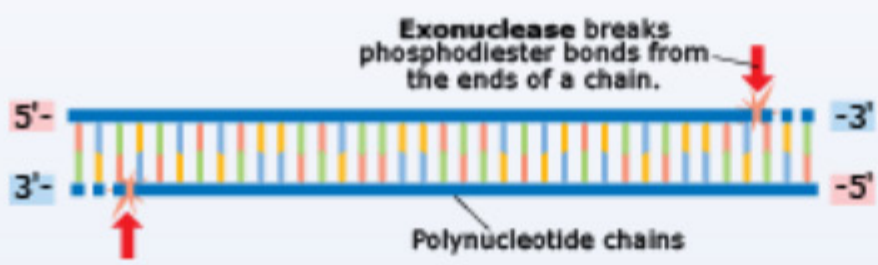
Nucleases are enzymes that cleave nucleic acid strands, and they have two varieties:

- *Endonucleases* cleave nucleic acid strands in the middle and can open up circular molecules. Bacteria put methyl groups over their restriction endonuclease sites to protect them from accidental cleavage. (Remember, bacteria don't have nuclear membranes!)



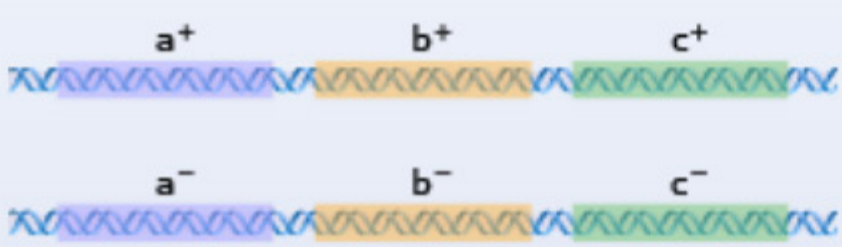
▲ **Figure 2-1.0C** Endonucleases

- *Exonucleases* cleave nucleic acid strands by sequential cleavage of nucleotides from the ends.



▲ **Figure 2-1.0D** Exonucleases

Alleles are alternative forms of the same gene.



▲ **Figure 2-1.0E** Alleles

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2 Bacterial Genetic Material

Bacteria have three types of DNA molecules possible in their cells, any and all of which may be transcribed and translated into protein to produce the phenotype of the cell.

2.1 Chromosome

- Usually only one but possibly with several copies
- Large, closed, circular (500 to 4,000 kb)
- Contains all essential genes

2.2 Plasmids

- Extrachromosomal genetic elements
- Small, closed, circular (400 kb)
- Replicate autonomously
- Genes are nonessential for life, but important in medicine because they are responsible for:
  - Fertility factors that allow bacterial conjugation
  - Most antibiotic resistances
  - Most exotoxins

2.3 Bacteriophages (Bacterial Viruses or "Phages")

Some bacteriophages—*temperate* or *lysogenic* phages—infect their host cells by integrating their genome into the bacterial chromosome. For as long as this stable association continues, the proteins encoded in the phage genome will be transcribed and translated along with the proteins encoded within the bacterial chromosome. This causes the expression of new traits (new proteins) in the bacterium and may affect pathogenesis by the process called *lysogenic conversion*. Traits acquired in this way will be inherited by bacterial progeny for as long as the stable association *(lysogeny)* continues.

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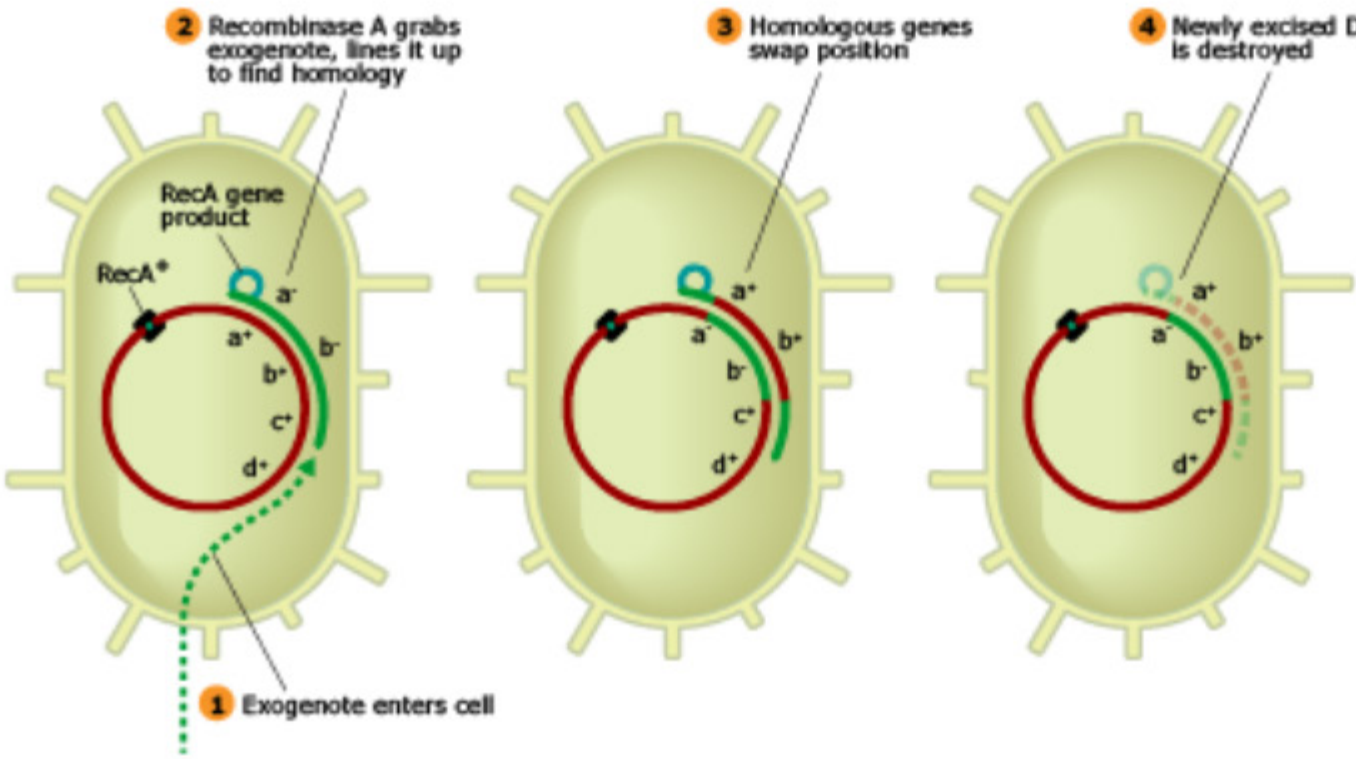
3 Stabilization of Donated DNA

Bacteria do not possess nuclei or nuclear membranes, so their DNA is susceptible to accidental cleavage and destruction by cytoplasmic enzymes. If a bacterium is to receive the donation of DNA from outside, that DNA must be quickly stabilized to avoid this immediate destruction. Bacteria have two means to protect DNA obtained from outside of their genomes: homologous and site-specific recombination.

3.1 Homologous Recombination

- A process to stabilize genes introduced into the cell cytoplasm *(exogenotes)* within the chromosome.
- The exogenote must be a short, linear piece of DNA with some sequence homology to that of the recipient chromosome.
- *Recombinase A* is the one absolute enzymatic necessity.
- The process causes a one-to-one exchange of the exogenote DNA with the chromosomal homologous DNA.
- The excised chromosomal DNA is destroyed by exonucleases.



▲ **Figure 2-3.1** Homologous Recombination

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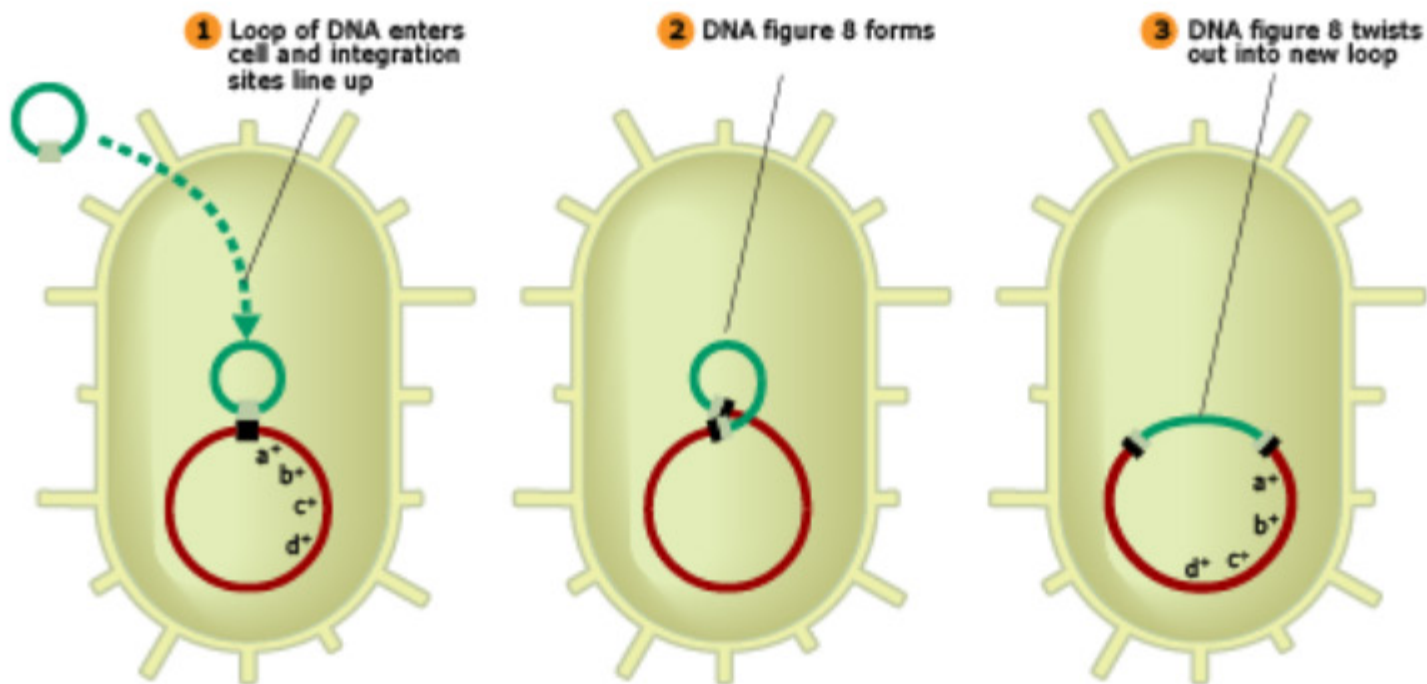
3.2 Site-Specific Recombination

- A process to integrate a small, circular DNA exogenote into the bacterial chromosome.
- Does not require true homology other than a *restriction endonuclease* site in common between the two DNA molecules.
- A mechanism to combine plasmids, temperate phage, and transposons into the chromosome (or a new location).
  - When plasmids integrate into the chromosome, they are called *episomes* and thus come under the control of chromosomal replication.
  - When temperate phages integrate into the chromosome of the host cell, they are called *prophages* and are similarly replicatively controlled.
  - *Transposons* are small mobile segments of DNA that move within bacterial cells to accumulate "pathogenicity islands" that can mediate expression of pathogenic features and drug resistances.
- No DNA is lost in the process.



▲ **Figure 2-3.2** Site-Specific Recombination

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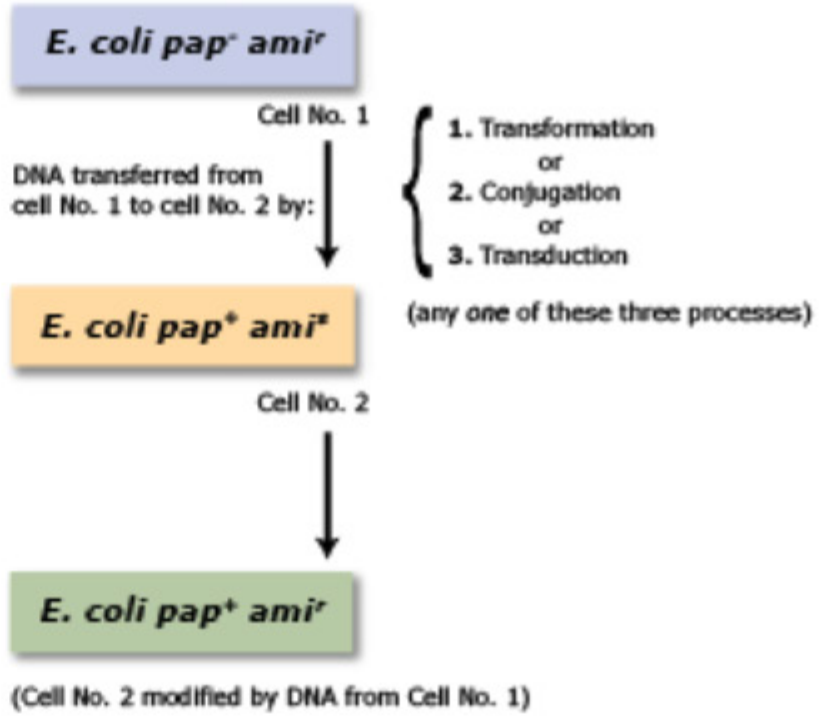
4 Gene Transfer

4.1 Overview

Bacteria reproduce by binary fission, an asexual process that ensures that genetic traits are passed from parent to progeny in a *vertical* fashion. Unless mutations occur, each progeny organism should receive an identical copy of the parental genome, so there is no mechanism for genetic exchange within this process. When early experiments proved that genetic exchange was possible between organisms *(horizontal transfer)*, a new set of mechanisms to explain these findings had to be discovered. These genetic exchange mechanisms are called *transformation*, *conjugation*, and *transduction*, and whenever such a genetic exchange results in a cell with improved survival ability, natural selection increases the proportion of such variant clones in the population.



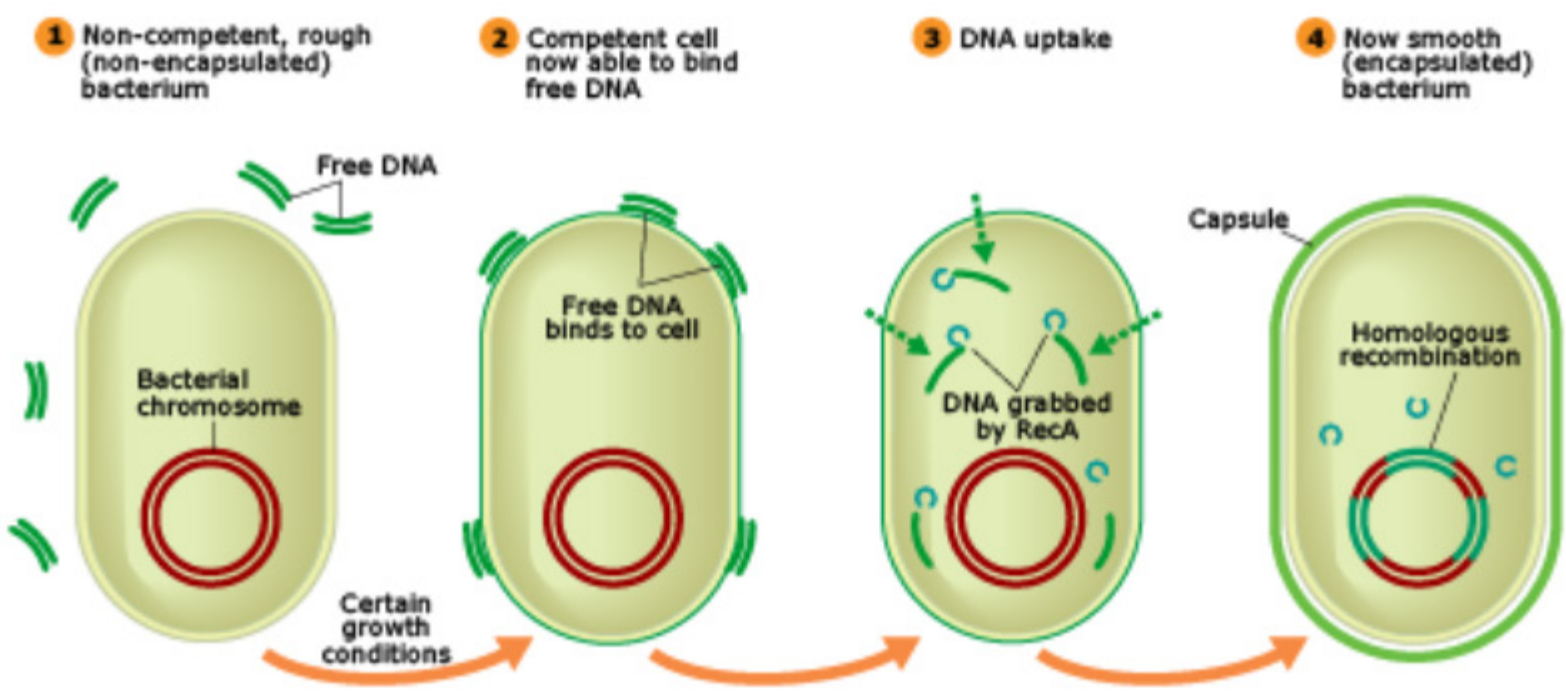
▲ **Figure 2-4.1** Gene Transfer

4.2 Mechanisms of DNA Exchange

4.2.1 Transformation

Transformation is the uptake of free DNA from the environment and its stabilization within the cell by homologous recombination.

- The recipient cell must first become competent, or capable of binding free DNA to its surface. Some cells do this naturally: the "natural transformers" such as *Bacillus* spp., *Haemophilus influenzae*, *Neisseria* spp., and *Streptococcus pneumoniae*.
- Once the free DNA is taken into the cell, homologous recombination is necessary if the donated DNA is to be stabilized.



▲ **Figure 2-4.2A** Transformation

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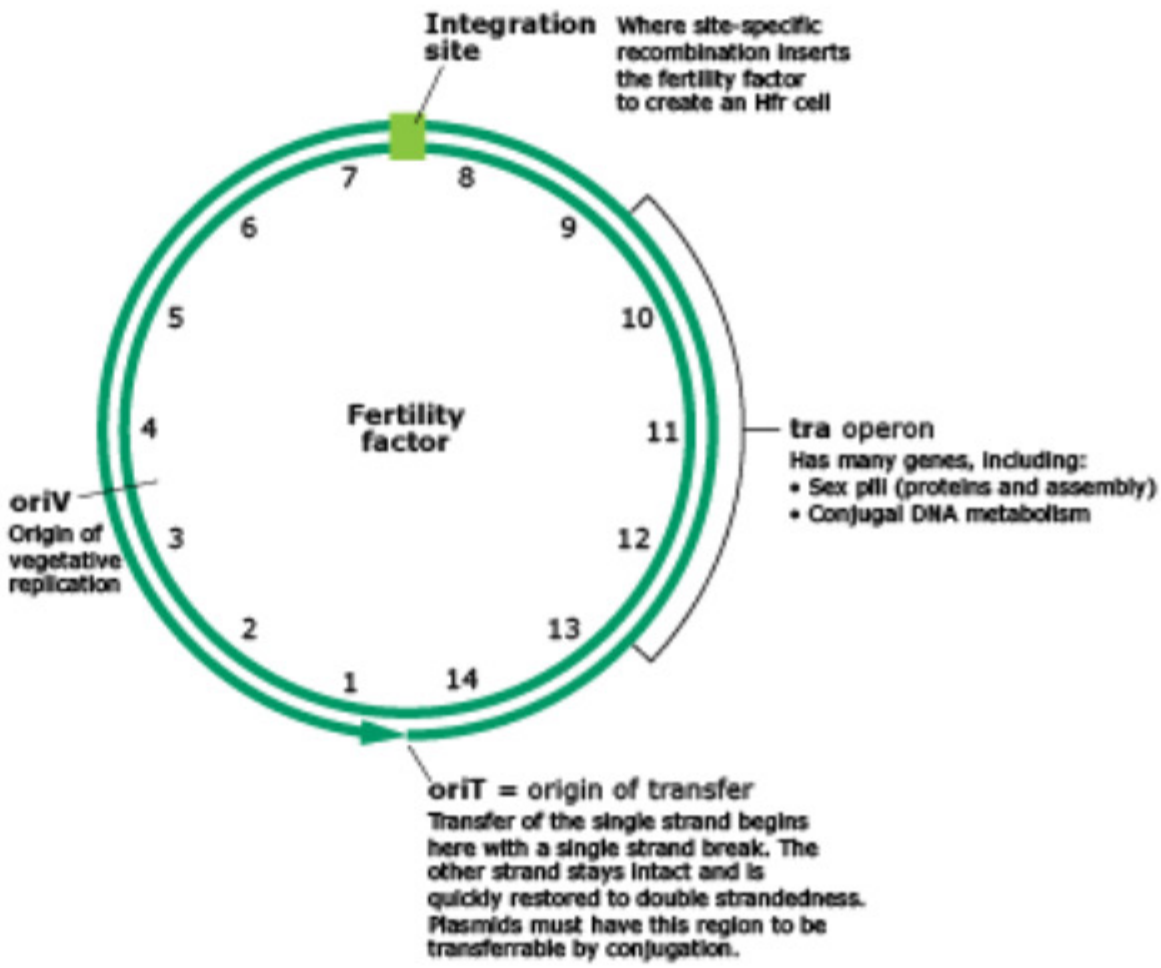
4.2.2 Conjugation

Conjugation is gene transfer from one cell to another using direct *cell-to-cell contact*. It is analogous to sexual exchange in eukaryotes in that it requires a male (donor) cell and a female (recipient) cell. The "gender" of a bacterium is determined by its possession of a *fertility factor*.

Fertility Factors These may exist as plasmids or may become integrated into chromosomal DNA by a variety of mechanisms. In either case, they may possess the following regions:

- **tra operon:** A region including many genes, all of which are necessary for the process of conjugation. If a cell has a tra operon, it becomes a donor in the exchange process. A cell without a tra operon is phenotypically a recipient.

  The genes encode:
  - Sex pili
  - Enzymes to direct conjugal DNA transfer
  - Products to stabilize mating pairs
- **oriT (origin of transfer):** The place where a break is made in one strand of the DNA so that it can begin to be unraveled into the recipient cell.
- **oriV (origin of vegetative replication):** The place where a replication fork is formed when the plasmid replicates its DNA. Plasmids replicate autonomously and are not under chromosomal control.
- **Integration site:** A region of genetic homology with the chromosome (a common restriction endonuclease site) that may allow the plasmid to become integrated into the chromosome by site-specific recombination. Not all fertility factors have integration sites, but those capable of chromosomal integration must have them.



▲ **Figure 2-4.2B** Fertility Factor

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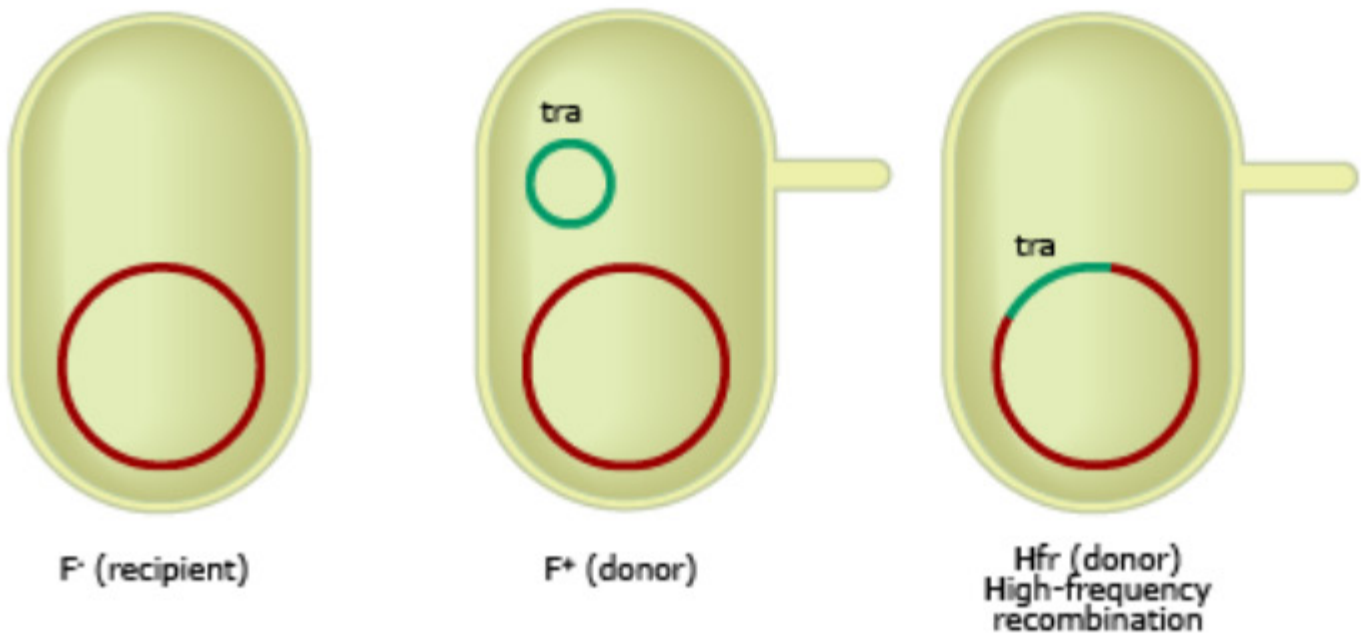
Bacterial Mating Types Three mating types for bacterial cells exist:

1. **F^- cells:** These cells entirely lack the fertility factor DNA and always serve as recipients in any conjugal cross.
2. **F^+ cells:** These cells possess the fertility factor in free plasmid form and act as donors of plasmid DNA.
3. **Hfr (high-frequency recombination) cells:** These cells have their fertility factor genes integrated into the chromosome as an episome and act as donors of *chromosomal* genes.



▲ **Figure 2-4.2C** Bacterial Mating Types

The F^+ and F^- Cross One type of conjugal cross involves the mating between an *F^+ (donor)* cell and an *F^- (recipient)*. In this cross, only *plasmid* DNA is transferred.

- The F^+ cell donor creates a modification of one sex pilus to become a *conjugal bridge* between the two cells.
- A break is made in a single strand of the fertility factor plasmid at *oriT*, and that strand is unraveled into the cytoplasm of the recipient cell.
- Because of the small size of the plasmid, for the purposes of Step 1, you can assume that one strand of the *entire plasmid* is transferred successfully.
- In each of the conjugating cells, the single-stranded plasmid DNA undergoes replication to produce identical double-stranded fertility factor plasmids in each of the cells.
- The recipient F^- cell, therefore, is now an F^+ donor.

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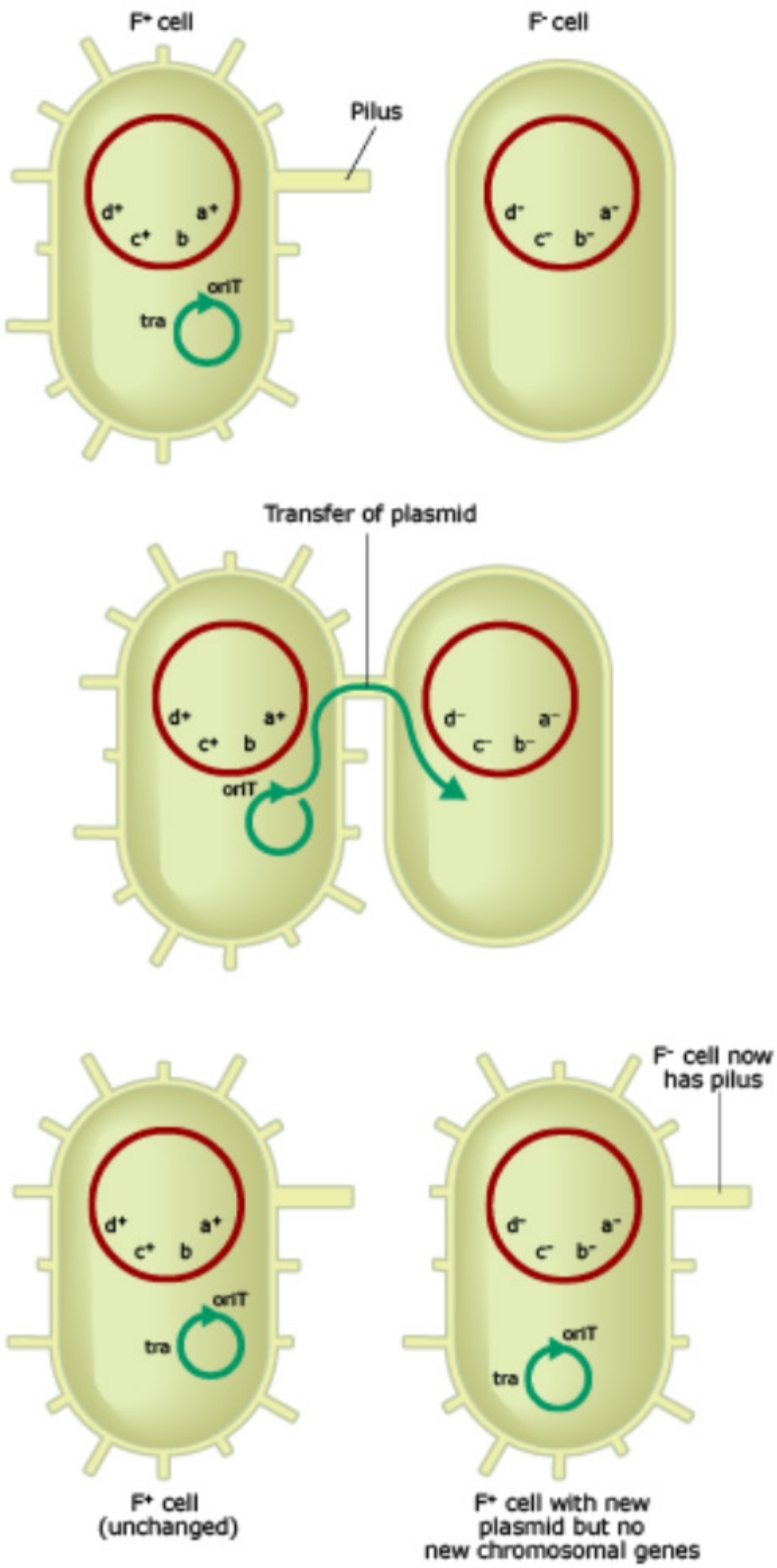

▲ **Figure 2-4.2D** $F^+ \times F^-$ Conjugation

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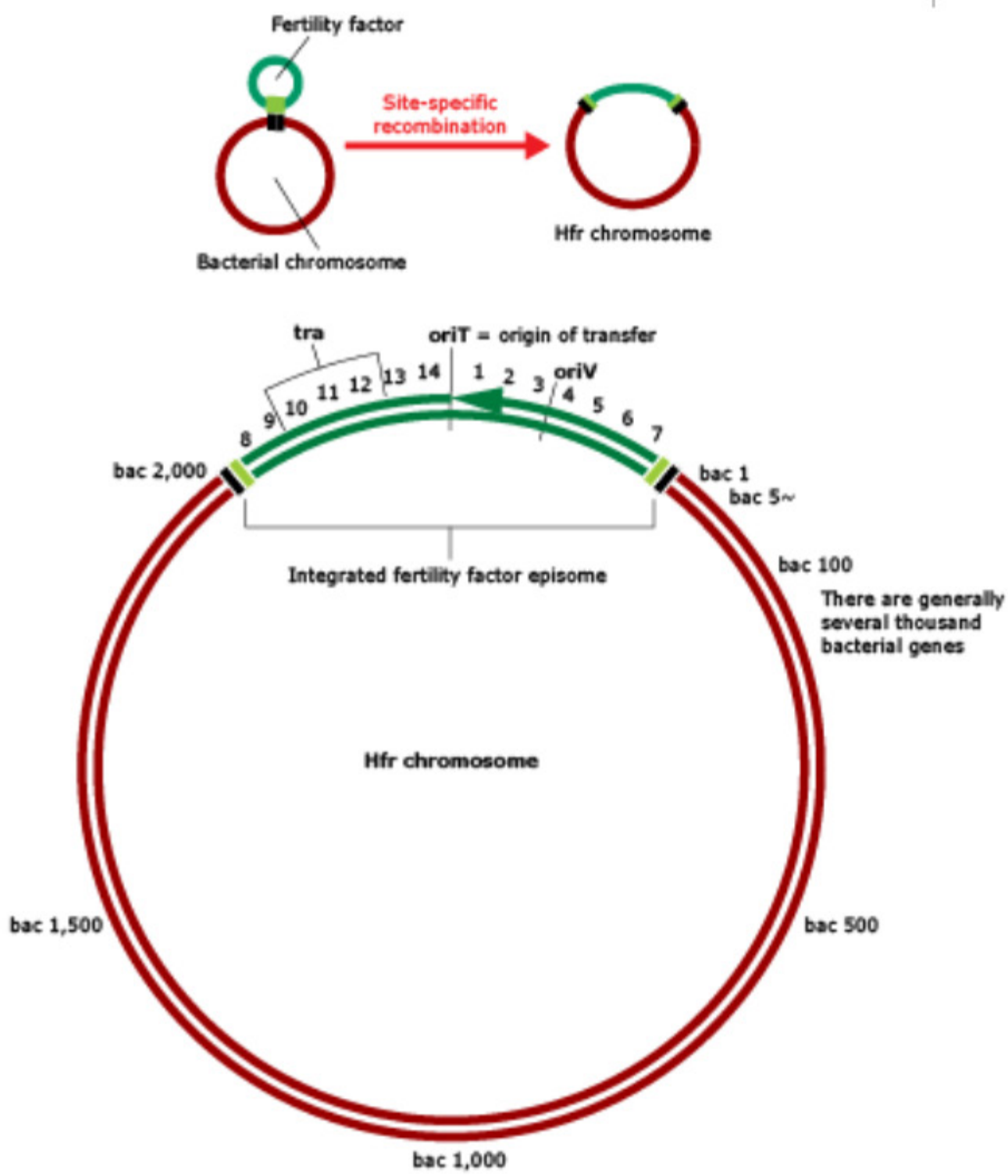
The Hfr and F⁻ Cross A second conjugal cross involves the Hfr cell as the donor and the F⁻ cell as the recipient. In this case, chromosomal genes are transferred from donor to recipient.

- **The Hfr Chromosome:** To understand the mechanism of this cross, it is necessary to review the process by which the Hfr chromosome arose. When fertility factor plasmids have integration site regions in common with a site on the bacterial chromosome, site-specific recombination can cause the two circles of DNA to become stably incorporated. Once this occurs, the two sides of the integration site—the original sticky ends—become the flanking sequences dividing DNA of plasmid origin from that of DNA of chromosomal origin. The sequence of DNA transfer in the cross, however, now follows the normal rule: oriT begins the process, followed in sequence first by plasmid origin genes and then chromosomal ones.



▲ **Figure 2-4.2E** The Hfr Chromosome

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- **The Conjugal Bridge:** The problem with transfer in this case, however, is a dual one: first, there is the fragility of the conjugal bridge, and, second, the large size of the entire Hfr chromosome. Because of these two factors, it is virtually impossible for the entire chromosome to cross the bridge before it is broken by Brownian motion in the culture vessel. The genes nearest oriT that make it across the conjugal bridge first are those most likely to be successfully transferred and stabilized.

Karsten Schneider/Science Source

▲ **Figure 2-4.2F** Conjugal Bridge

- **The Donation of DNA:** The process of the Hfr × F^- conjugal cross begins again, with the formation of a conjugal bridge between donor and recipient. Next:
  - A break is made in one strand of the DNA duplex at oriT, which begins to pass across the conjugal bridge.
  - Initially, plasmid genes from the episome are carried through the bridge, but then chromosomal genes follow in order.
  - Because the entire Hfr chromosome is at least 100 times the size of the F plasmid, the bridge breaks before the transfer is complete, trapping a single-stranded linear piece of DNA of both episome and chromosome origin in the recipient cell.
  - The Hfr cell replaces the donated strand of DNA by replication and its genotype is unchanged by the process.
  - The recipient cell must now be capable of homologous recombination for the stabilization of donated genes to be possible.
  - Because the F^- recipient has no DNA homologous to that of the episome, the only DNA that can be successfully homologously recombined is that from the chromosome of the Hfr donor.
  - Therefore, it is simply a statistical probability that the chromosomal genes closest to oriT are those most likely to be successfully saved.
  - At the end of the process, the F- cell has acquired new chromosomal alleles from the Hfr cell, but remains a recipient phenotypically.

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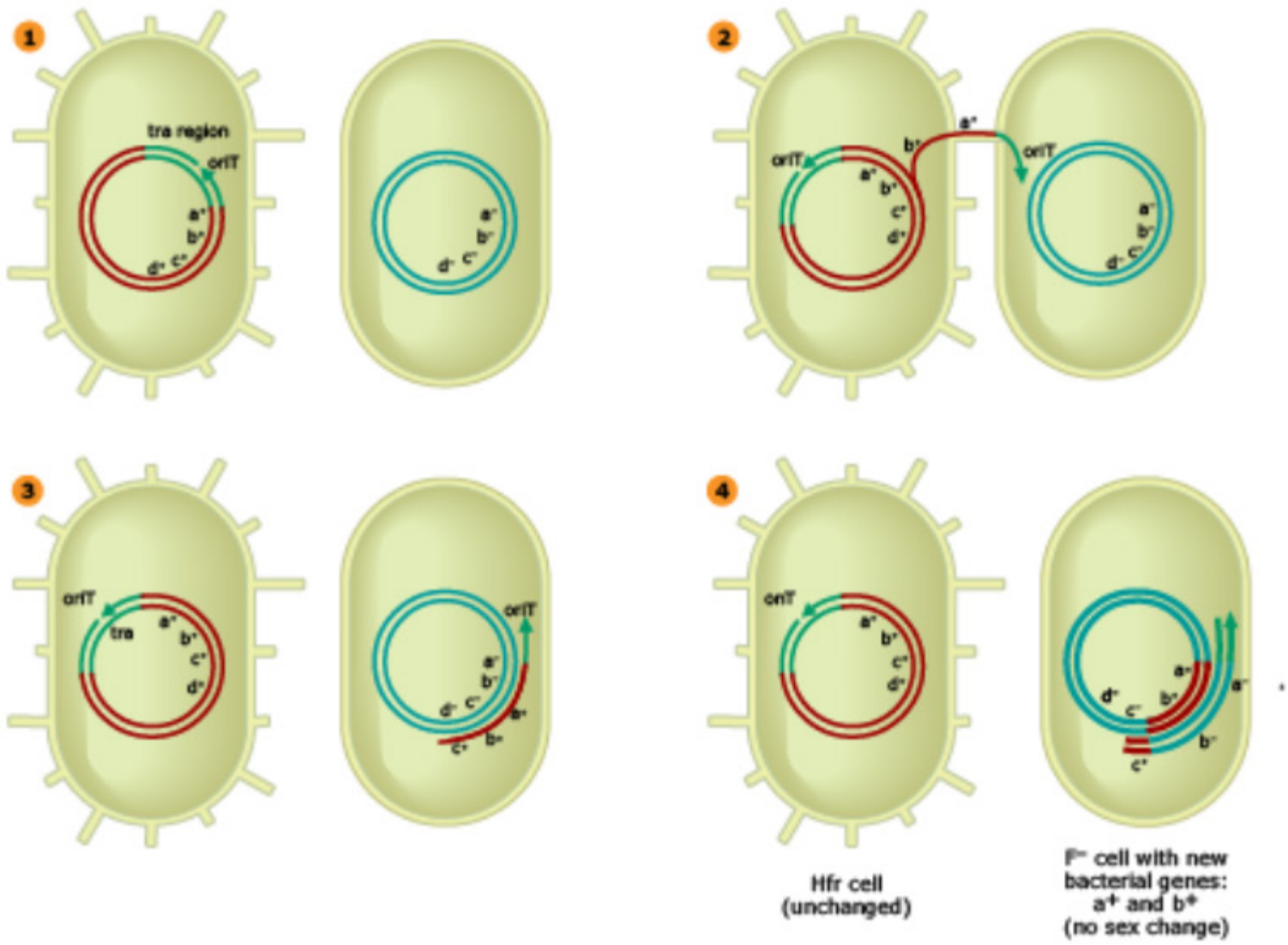

▲ **Figure 2-4.2G** The Hfr × F⁻ Cross

4.2.3 Transduction

Transduction is defined as the transfer of DNA from one bacterium to another using a phage as a vector. There are two forms of transduction, both of which may occur as an error of the phage life cycle.

Generalized Transduction

The Lytic Phage Life Cycle Bacterial viruses may exhibit two types of life cycles: *lytic (virulent)* or *lysogenic (temperate)*. The lytic phage life cycle runs a rapid course:

- Attachment to the bacterial cell and injection of phage DNA
- Destruction of bacterial DNA and use of cellular machinery to produce phage proteins
- Replication of phage genome and assembly of phage particles
- Release of phage particles by cell lysis

The Accident of Generalized Transduction Sometimes, as an accident of this life cycle, a piece of bacterial DNA rather than a viral genomic copy gets loaded into a developing phage head. This creates a *generalized transducing phage*: a virus particle that is incapable of repeating its life cycle, but is still capable of delivering and injecting its DNA into a new bacterial cell. The injection of this linear piece of DNA picked up accidentally from the first infected cell must now undergo homologous recombination if it is to be saved inside that cell.

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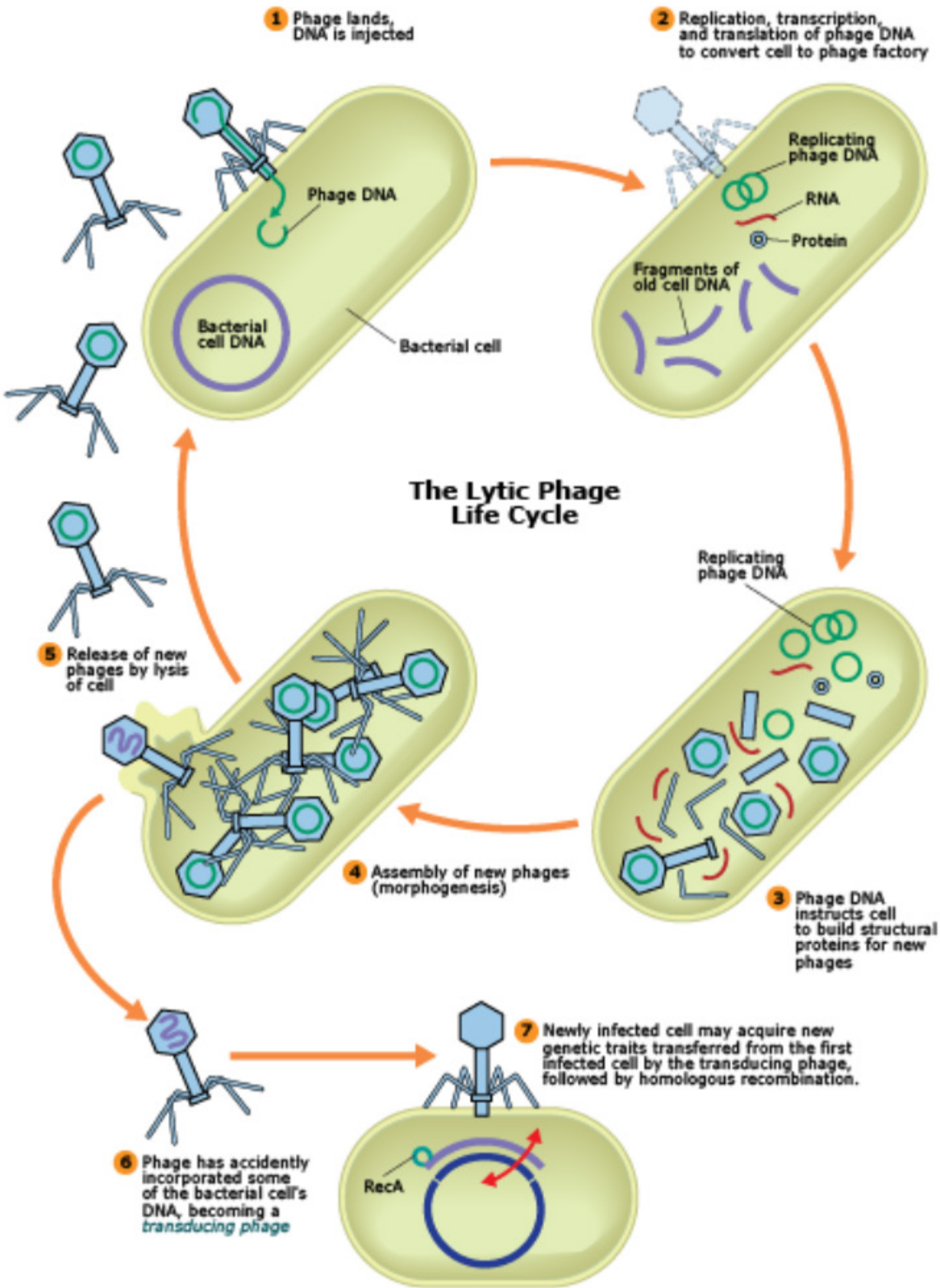

▲ **Figure 2-4.2H** Generalized Transduction

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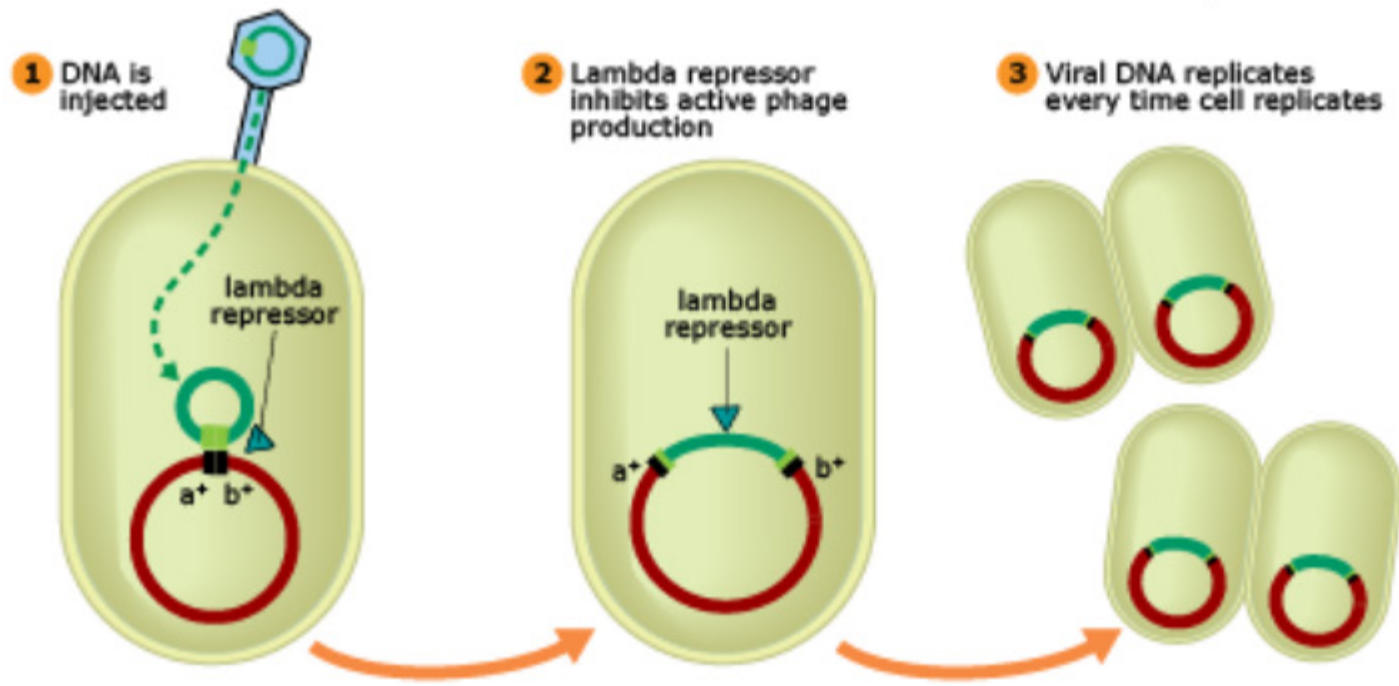
Specialized Transduction

The Temperate Phage Life Cycle A bacterial virus that undergoes a period of stable association with the bacterial genome is said to be a *temperate* or *lysogenic phage*.

- **Integration:** The first step of the temperate phage life cycle again involves attachment to the bacterial cell and injection of DNA. Next, however:
  - The injected DNA circularizes and integrates into the chromosome at a specific integration site by site-specific recombination.
  - If a *repressor protein* encoded in the phage genome is produced rapidly enough, the phage remains stably integrated into the chromosome, and the viral DNA is under the replicative control of the bacterial chromosome: Binary fission of one *lysogenized cell* produces identical lysogenized progeny.



▲ **Figure 2-4.2l** Integration

- **Induction and Normal Excision:** If something happens to damage the repressor gene of the temperate phage, the virus goes into a phase of lytic replication. This can happen naturally or can be induced by cold, ultraviolet light, or some alkylating agents.
  - Once the repressor protein is no longer produced, viral structural proteins begin to be assembled.
  - Viral DNA is excised from the chromosome by lining up the integration sites, reversing the mechanism by which the phage integrated into the chromosome. This is referred to as *normal excision*.
  - Viral genomic DNA is replicated and loaded into the phage heads.
  - Lysis of the cell releases a new generation of normal temperate phage to complete the life cycle.

Important Concept

The process of lysogeny can give bacteria new pathogenic traits, and these are highly tested in Step 1. Bacteria that have acquired new pathogenesis in this fashion are said to have undergone *lysogenic conversion*.

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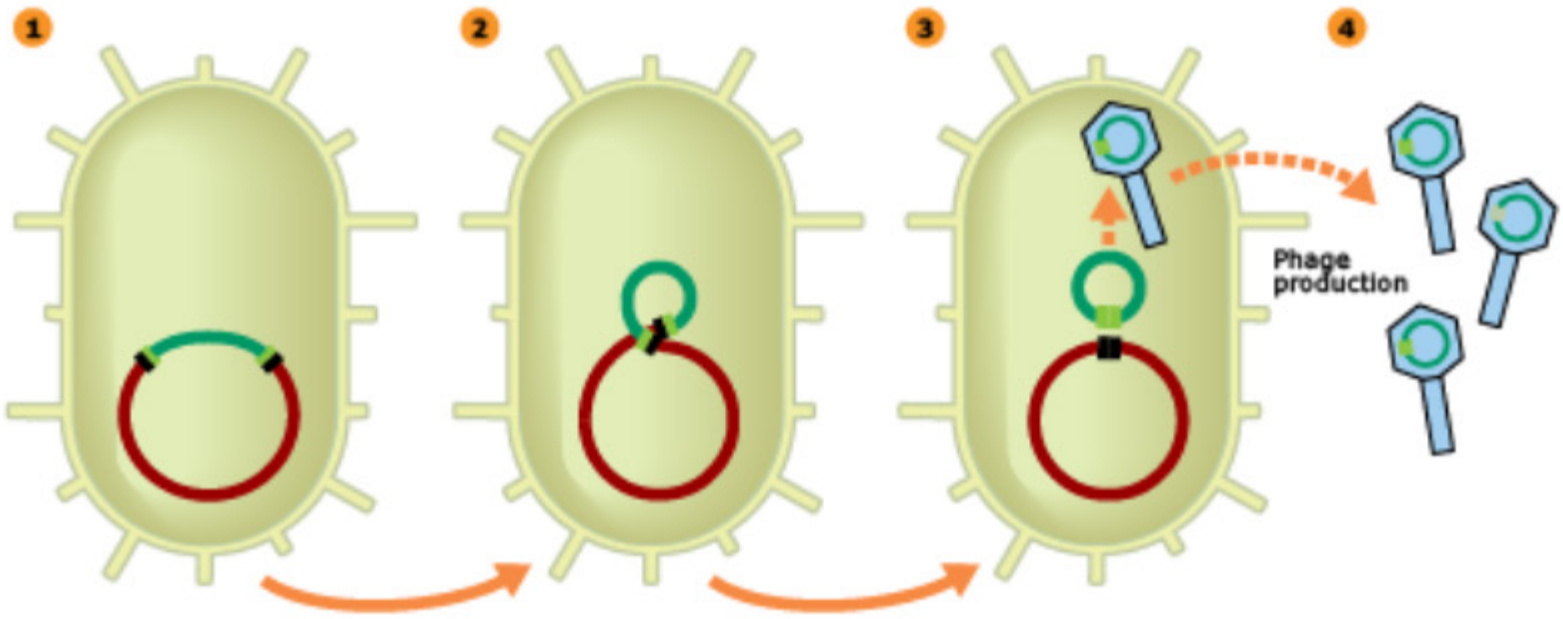


▲ **Figure 2-4.2J** Normal Excision

The Accident of Specialized Transduction Sometimes, as an error of the lysogenic life cycle, excision error can lead to *specialized transduction*.

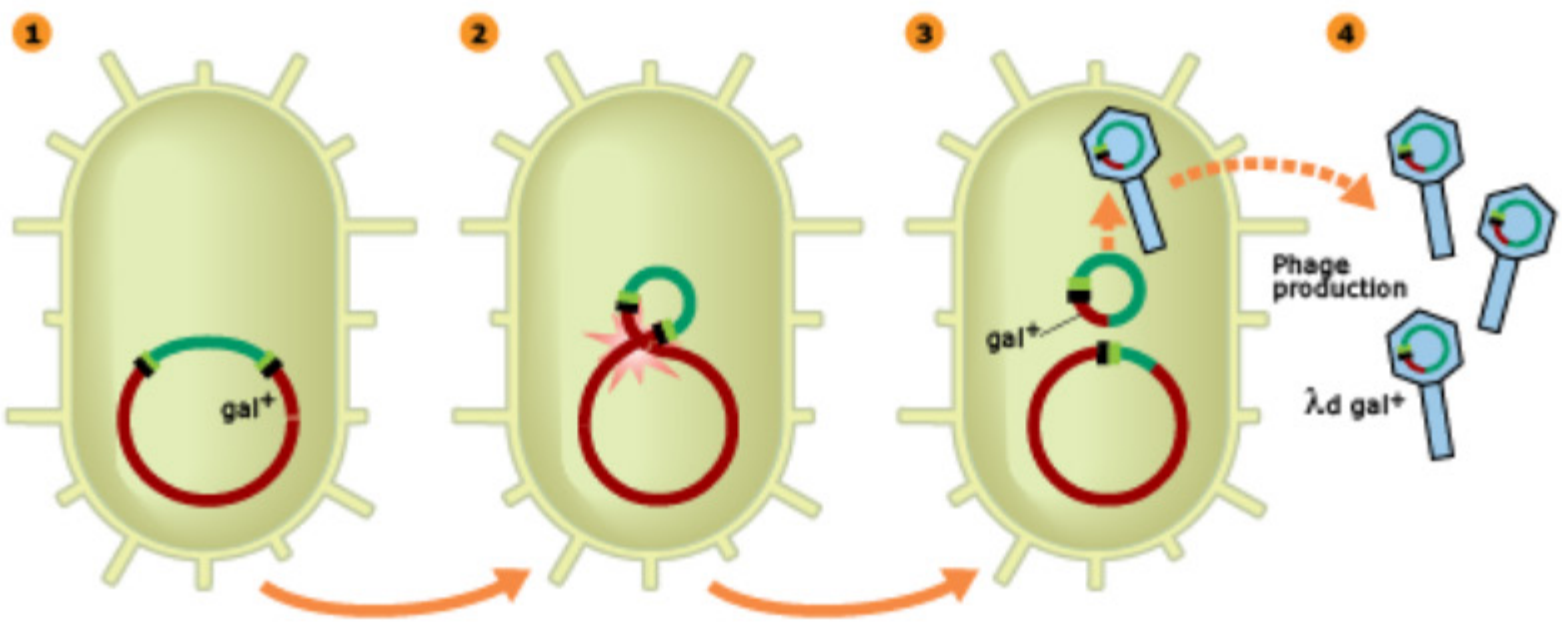
- **Error of Excision:** When the two ends of the integration site of the integrated phage fail to realign during the excision process, portions of bacterial DNA can be included in the departing virus DNA. Conversely, portions of viral DNA also can be left behind in the bacterial chromosome. This is referred to as an *error of excision*. Although in the short term, phage progeny are produced, culminating the lytic phase of the life cycle, the progeny viruses produced are *defective phages* by virtue of having left some of their essential genomic DNA behind in the lysed bacterial cell. Because the integration site of the phage is a defined site, only bacterial chromosomal genes near the integration site may be accidentally picked up in this way.

Memory Aid

Pathogenic traits of bacteria known to result from lysogenic conversion include:

L—Labile toxin of ETEC
O—O antigen of *Salmonella*
V—Verotoxin of EHEC
E—Erythrogenic exotoxins of *Streptococcus pyogenes*
D—Diphtheria toxin
C—Cholera toxin
B—Botulinum exotoxin
S—Shiga toxin

LOVED CBS or, in other words, if a person is *LOVED*, that *C*an *B*ring *S*equelae (like pregnancy, and these bacteria are pregnant with bacteriophages).



▲ **Figure 2-4.2K** Error of Excision

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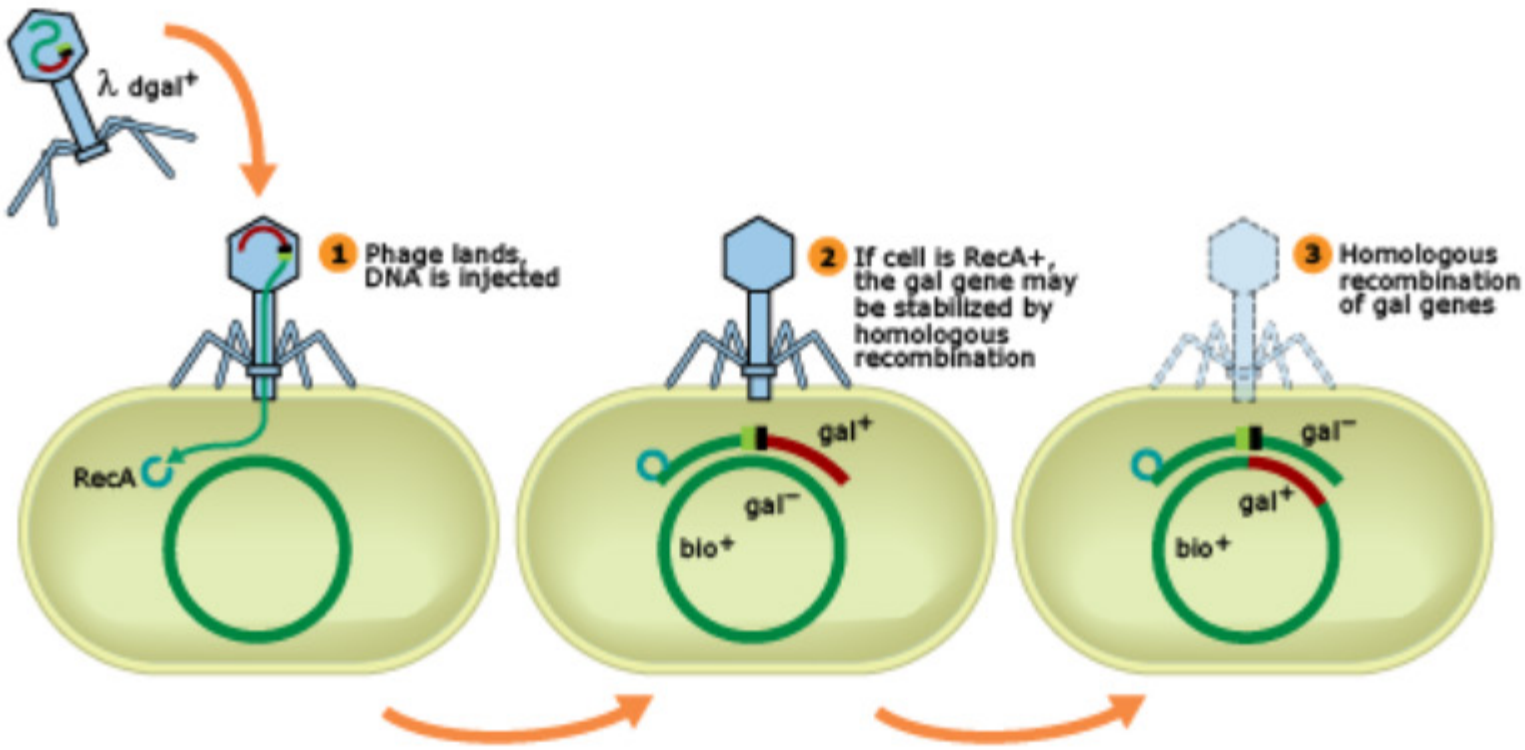
- **Delivery of Genetic Information:** The defective phages created at the end of the error of excision cannot complete their life cycles. They cannot produce another generation of viral progeny because they have lost, in the first infected cell, crucial genes for their existence. However, they are now *specialized transducing phages*, capable of delivering the DNA acquired from the first infected bacterial cell to another cell. They are said to be "specialized" in their transduction because they are capable of picking up and delivering only genes that were close to the integration site of the original phage, so it is possible to predict what traits may be transmitted.
  - Specialized transduction begins with the attachment of a defective phage to a new bacterial cell.
  - Phage and bacterial DNA are injected into the new cell, but because of the error of excision, the DNA introduced is now linear (one-half of the sticky ends were left behind in the first infected cell, so circularization is not possible).
  - The recipient cell must be capable of homologous recombination to stabilize the newly introduced DNA.
  - Because homologous recombination requires homology, the only potential recombination that can occur is to stabilize DNA acquired from the first bacterium. Phage genes are non-homologous and are destroyed by exonucleases.
  - The second bacterium now acquires new genetic traits, delivered from another bacterial cell, via a lysogenic phage.

Memory Aid

- Think of the "F" in transFormation as meaning Free DNA.
- Think of the "D" in transDuction to remind you of Delivery of DNA by a phage.



▲ **Figure 2-4.2L** Specialized Transduction

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4.3. Summary Comparison of Mechanisms of Genetic Exchange

▼ **Table 2–4.3** Mechanisms of Genetic Exchange

Type of Exchange	Mechanism	Genes Transferred	Recombination Required	Competency Required	Comments
Transformation	Free DNA	Any	Yes, homologous	Yes	Sensitive to extracellular nucleases
$F^+ \times F^-$ Conjugation	Cell-to-cell transfer of plasmid DNA	Fertility factor	No, plasmids are circles and intrinsically stable	No	Gender change in recipient
Hfr × F^- Conjugation	Cell-to-cell transfer of chromosomal DNA	Chromosomal, nearest to oriT	Yes, homologous	No	No gender change in recipient
Generalized Transduction	Accident of packaging in the lytic virus life cycle	Any	Yes, homologous	No	Requires previous lytic phage infection
Specialized Transduction	Error of excision in a lysogenic virus life cycle	Chromosomal, near to integration site of phage	Yes, homologous	No	Requires previous lysogenic phage infection

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5 Drug Resistance

The mechanisms of horizontal genetic exchange discussed above are crucial in the evolution of drug-resistant strains of bacteria that are now capable of surviving many of our first-line antibiotic therapies. Bacteria will always be able to evolve resistance mechanisms more rapidly than humans can develop new drugs, so global understanding of these emerging resistances is critical. In the case of vancomycin-resistant *Staphylococcus aureus* (VRSA) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP), therapeutic options are extremely limited, and concern that these resistances may spread globally throughout microorganisms is significant. Microbial drug resistances may be broadly categorized into three forms: *intrinsic*, *chromosome-mediated*, and *plasmid-mediated*.

5.1 Intrinsic Drug Resistance

When an organism is said to have *intrinsic drug resistance*, it is generally because that organism lacks the target molecule for a drug. This is a trait intrinsic to the anatomy and physiology of the organism and is generally not iatrogenic.

- *Mycoplasma* is intrinsically resistant to penicillin and cephalosporins because the genus lacks a cell wall, and peptidoglycan destruction is the mechanism of action for such drugs.
- All bacteria that lack mycolic acids are said to be intrinsically resistant to isoniazid because that drug targets mycolic acids.

5.2 Chromosome-Mediated Drug Resistance

Drug resistance genes encoded on bacterial chromosomes generally encode *structural proteins* that, when altered, affect the binding of the drug. The most medically important example of a chromosome-encoded drug resistance is the gene that has given us *methicillin-resistant Staphylococcus aureus (MRSA)*. In this case, a mutation in a penicillin-binding protein (PBP) arose spontaneously as early as two years after the introduction of methicillin in 1959. Since that time, natural selection favoring resistant strains has caused the proportion of resistant *Staphylococcus aureus* strains isolated in hospitals and nursing homes to rise toward 95% worldwide.

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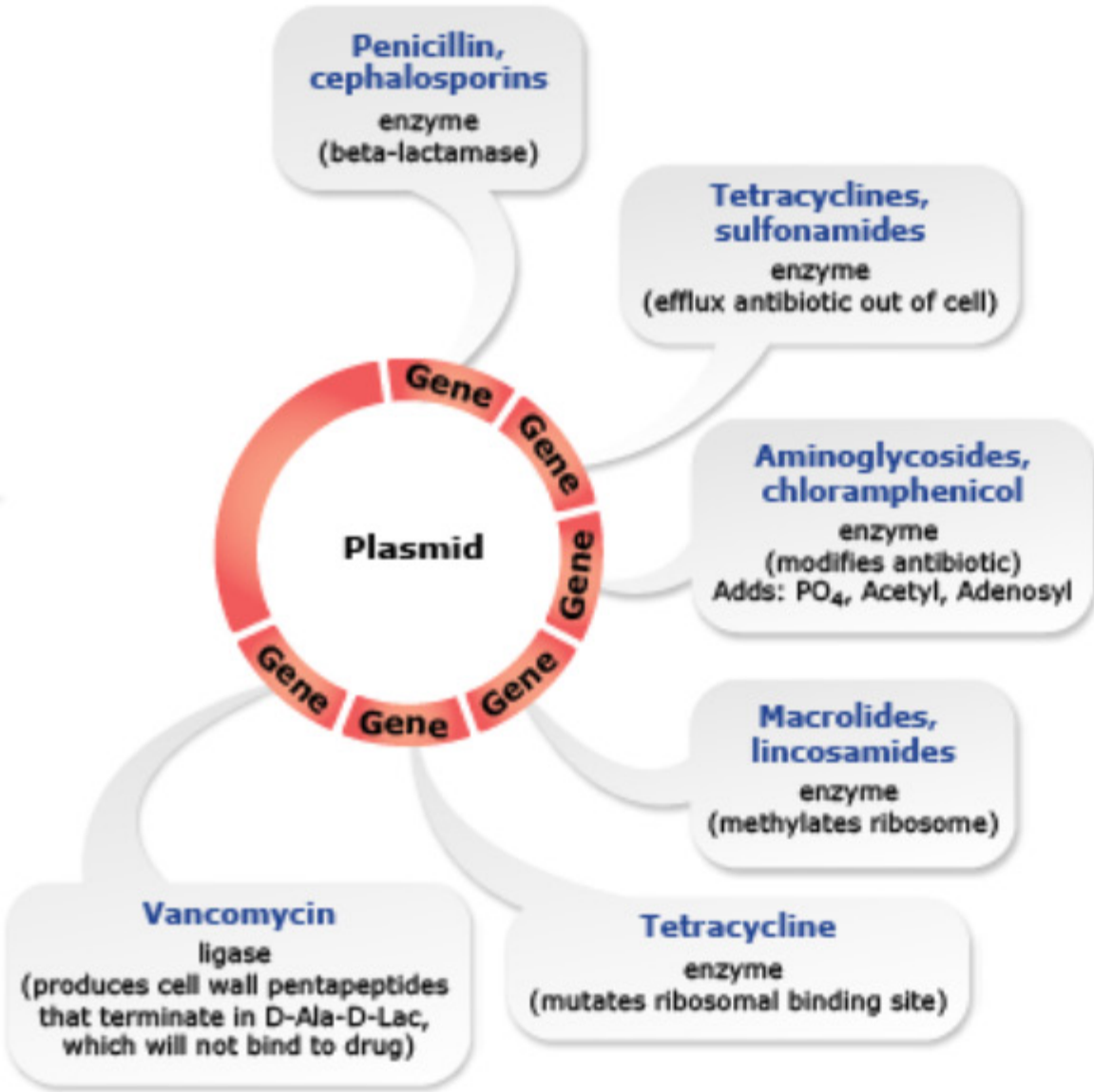
5.3 Plasmid-Mediated Drug Resistance

The drug resistance genes found on plasmids generally encode *enzymes* that modify the drug. Because of the ease with which plasmids are traded among groups of bacteria, these resistances spread through populations. A summary of the known plasmid-encoded drug resistance mechanisms is shown in the figure below.



▲ **Figure 2-5.3A** Plasmid-Encoded Drug Resistance Mechanisms

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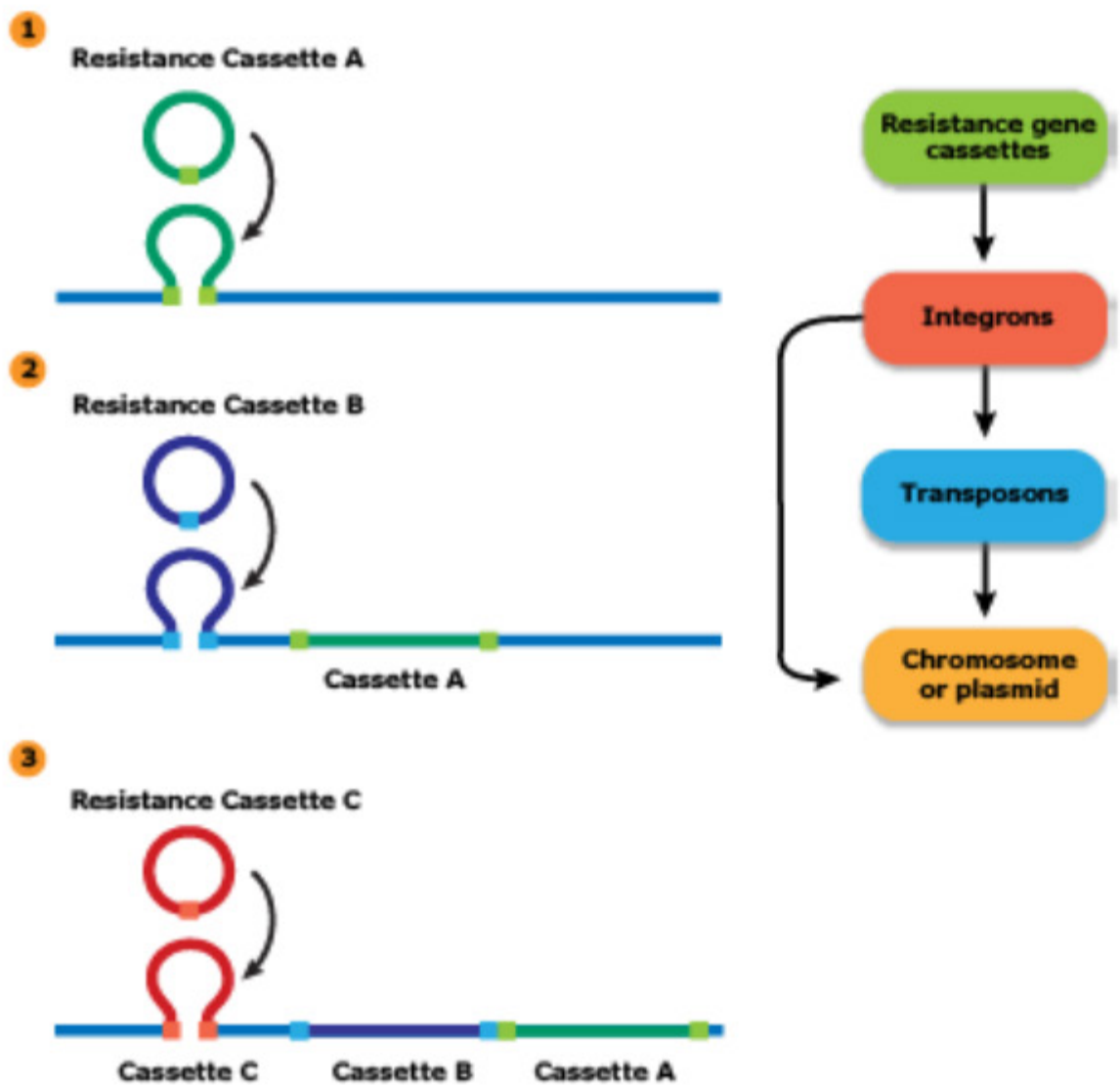
5.3.1 Accumulation of Multiple Drug Resistance Genes

Another alarming discovery in recent decades is that bacteria have mobile genetic elements that can collect multiple drug resistance genes in a compact region of DNA. These mobile elements are defined on the basis of their size.

- The smallest of these mobile elements are referred to as *gene cassettes*. These normally contain only one gene and an additional short sequence that functions as a specific recombination site.
- An *integron* is defined as a genetic element that contains a site at which gene cassettes can be integrated by site-specific recombination.
- An *insertion sequence* is the smallest transposable element. It consists of a gene encoding the transposase enzyme, including promoter and transcription and translation termination signals, flanked by indirect repeats.
- A *transposon* is an insertion sequence containing additional DNA sequences.



▲ **Figure 2-5.3B** Accumulation of Drug Resistance Genes

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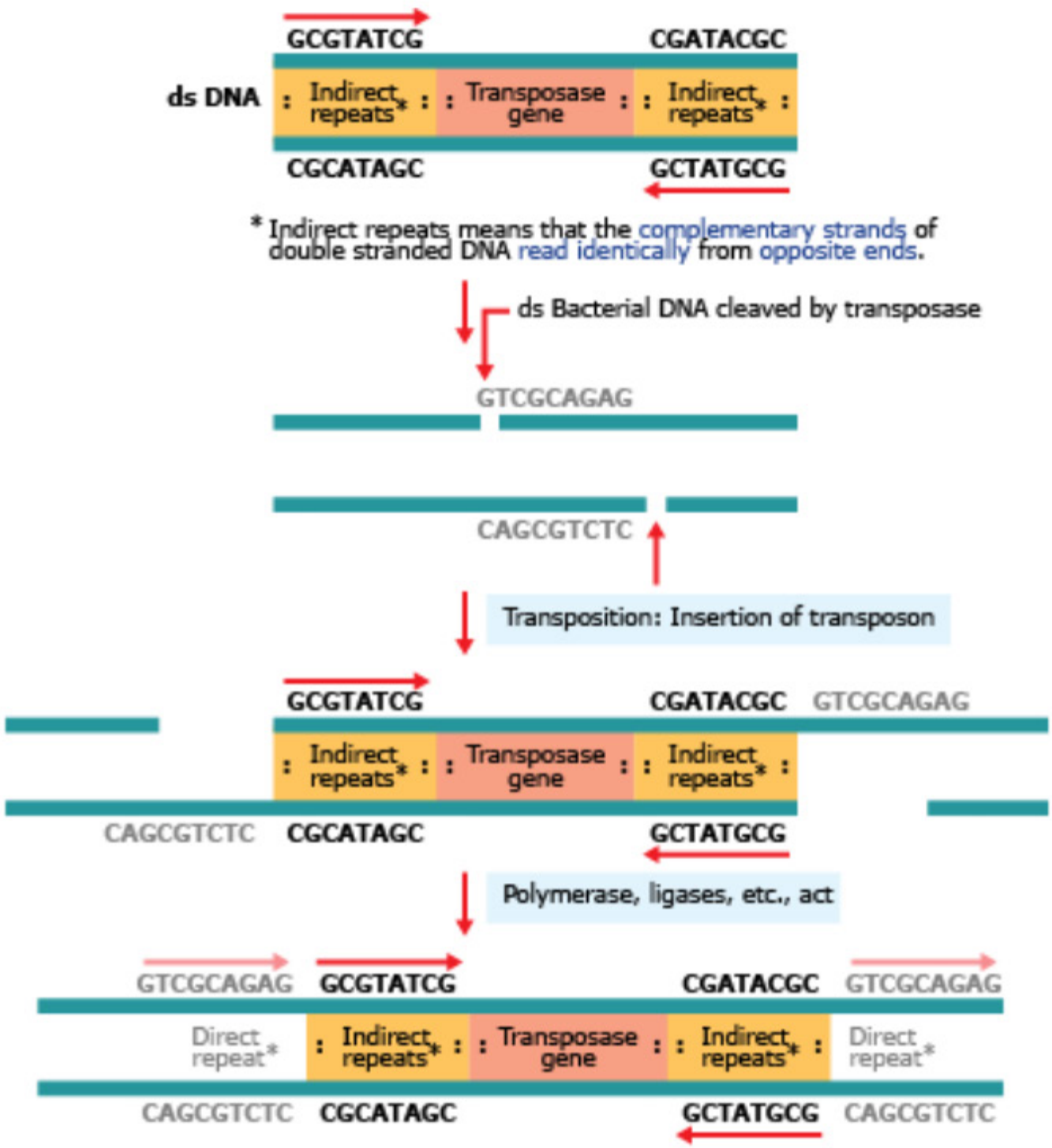
5.3.2 Transposition

Transposition is the mechanism by which both insertion sequences and transposons move within cells. It is a cut-and-paste mechanism that may be *replicative* and create multiple copies within the cell, or *conservative*, in which case the single copy is simply moved from place to place.

- Transposable elements are identified by the possession of *indirect (inverted) repeats* of nucleotides on each of their ends. These are sequences that read identically left to right on the top strand and right to left on the bottom strand.
- When the transposase enzyme lifts the element out of its original location, it creates a *staggered cut* in a new location, and cuts and pastes the transposon into that spot.
- The two ends of the staggered cut are then repaired to create *direct repeats*—sequences of nucleotides that are exactly superimposable—as flanking sequences at the point of integration.



▲ **Figure 2-5.3C** Transposition

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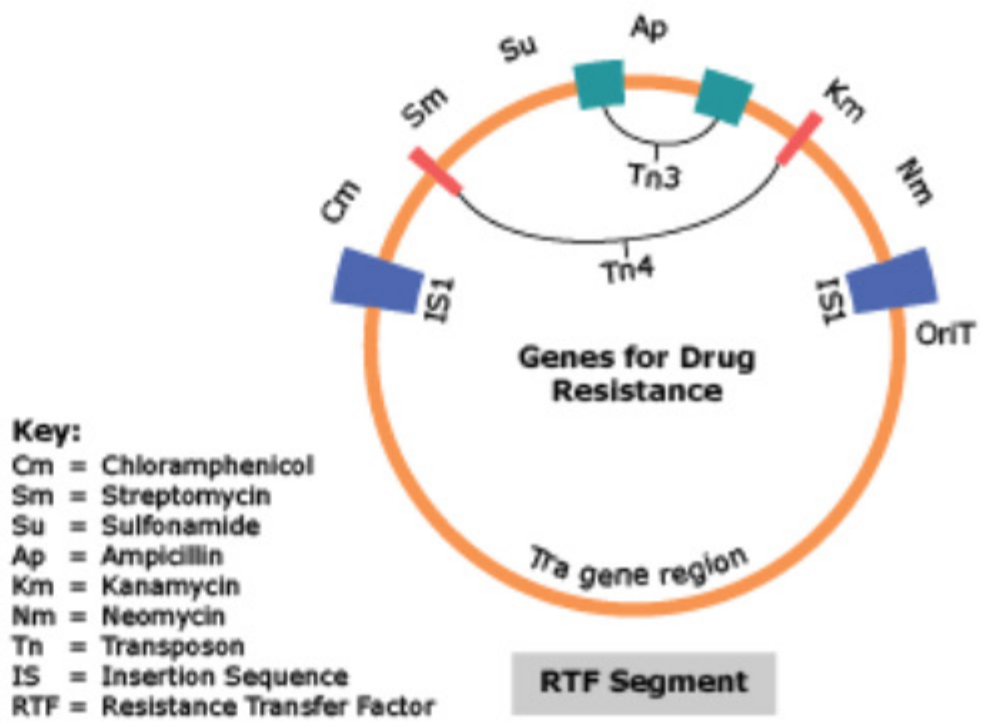
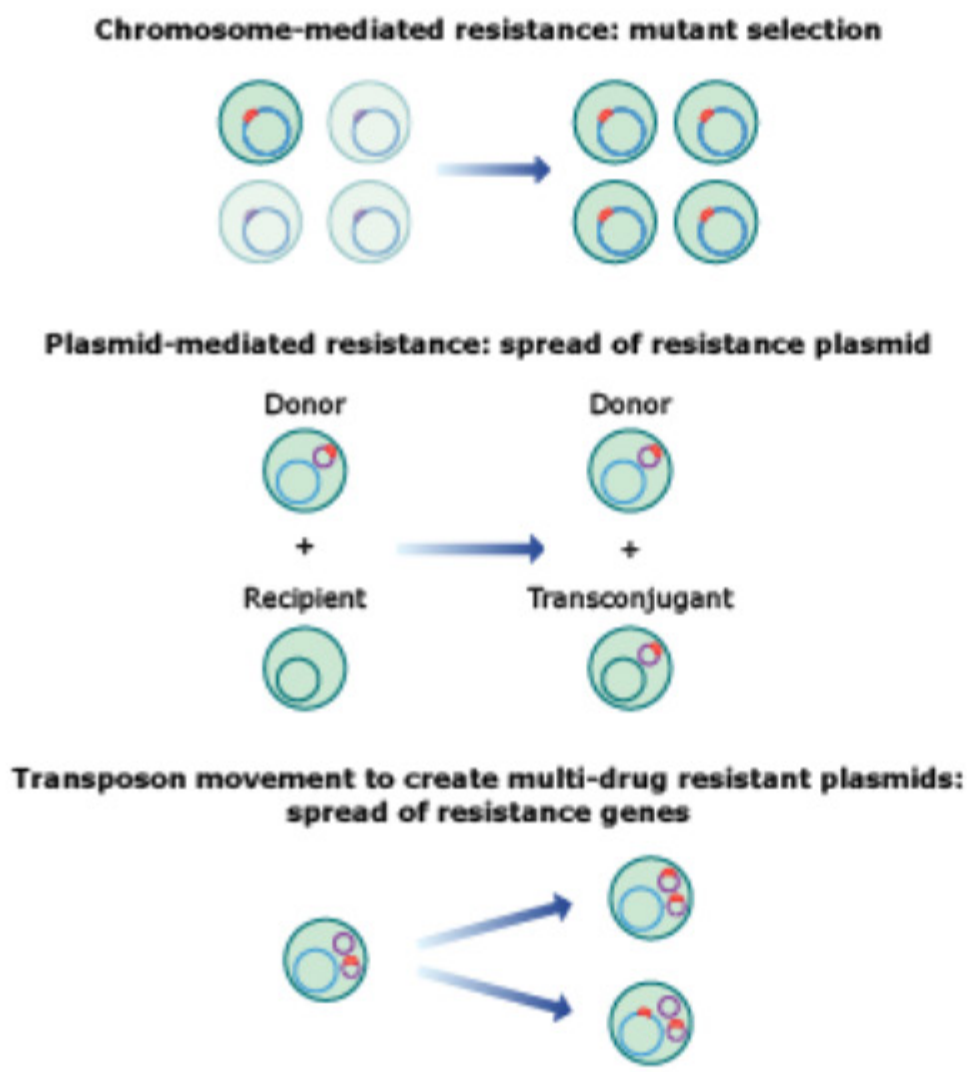
The accumulation of transposable elements in locations such as fertility factor plasmids—where their transmission to other bacteria via conjugation becomes likely—has created a growing number of known *resistance transfer factors*. One of these, which has given us vancomycin-resistant enterococcus (VRE), has been shown to have 20 drug resistance genes as well as genes that promote resistance to six of the most commonly used hospital disinfectants.

It is the overuse and misuse of antibiotics that causes bacteria to evolve to resist these chemicals. Once the mutations occur, natural selection dictates that strains resistant to drugs and disinfectants will survive and multiply to become larger and larger proportions of the population.



▲ **Figure 2-5.3D** Resistance Transfer Factor



▶ **Figure 2-5.3E** Selection of Resistant Strains

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5.3.3 Summary of Major Mechanisms of Genetic Transfer

▼**Table 2–5.3** Mechanisms of Genetic Transfer

Mechanism	Organism	Gene/Drug
Transformation	*Streptococcus pneumoniae*	Penicillin-binding protein mutations
Conjugation	Gram-negative bacilli	Most resistances
	Staphylococcus aureus	Vancomycin resistance
Conjugation using non-conjugative plasmids via mobilization	*Neisseria gonorrhoeae*	Most resistances
Transduction	*Staphylococcus aureus*	Methicillin resistance

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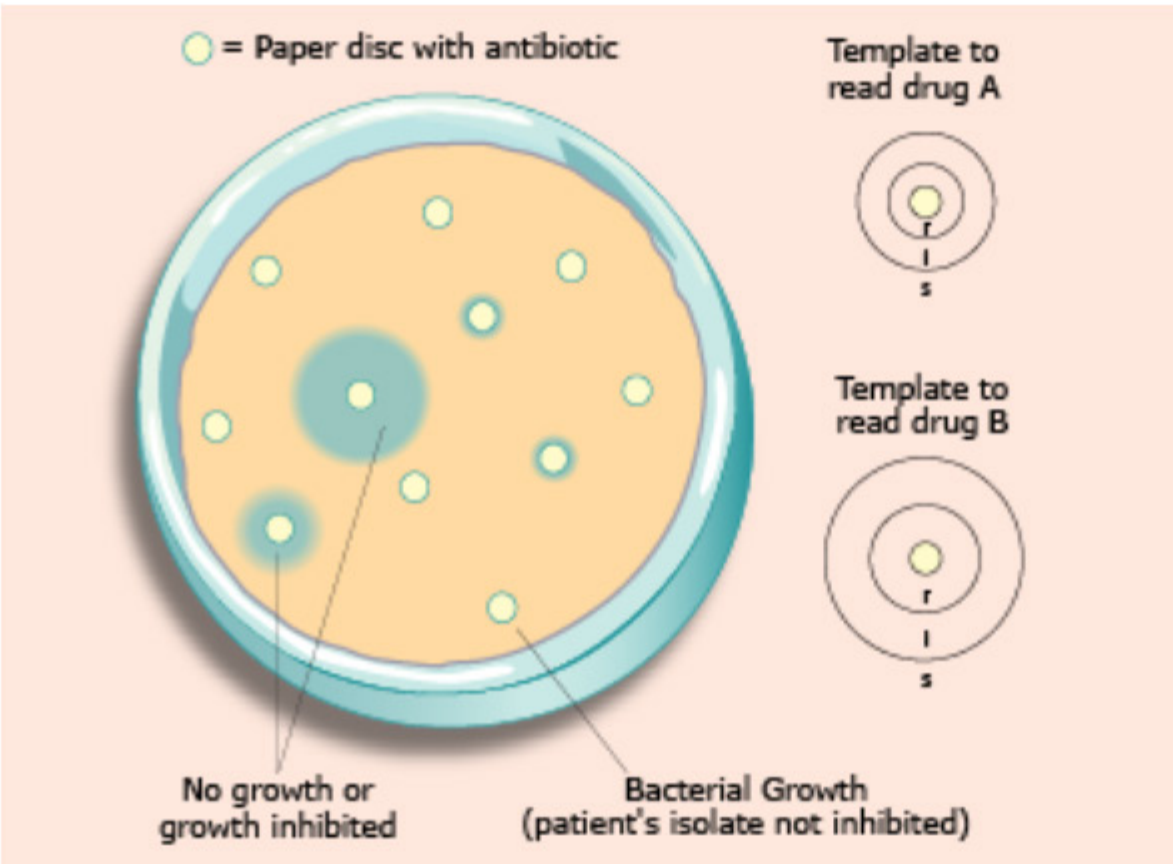
6 Antibiotic Susceptibility Testing

6.1 Kirby-Bauer Agar Disc Diffusion Test

The first step in determination of antibiotic susceptibility is usually the *Kirby-Bauer agar disc diffusion test*. In this rapid screening test, large numbers of antibiotics are tested against the patient's isolate. It suffers from giving only a qualitative result, but has the advantage of being relatively inexpensive and easy to perform.

- An agar plate is produced with a confluent lawn of bacteria from the patient.
- A dispenser drops multiple filter paper discs impregnated with a variety of antibiotics at various concentrations onto the surface of the agar plate.
- The plate is incubated, allowing diffusion of the drugs out of the filter paper to create a concentration gradient for each drug.
- The diameter of the zone of inhibited bacterial growth around the disc is compared to a key provided with the kit.
- The results are noted as *resistant*, *intermediate*, or *sensitive* to the drug.



▲ **Figure 2-6.1** Kirby-Bauer Agar Disc Diffusion Test

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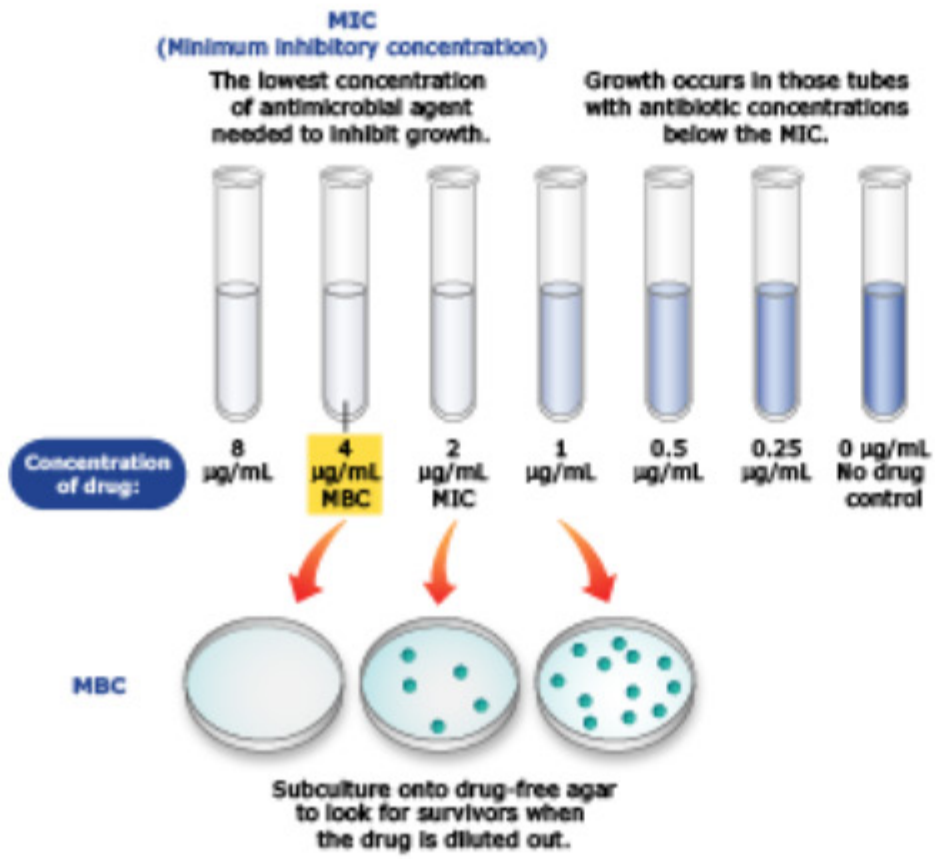
6.2 Minimal Inhibitory Concentration (MIC)

Once it is established that a drug is effective against the patient's isolate, the *minimal inhibitory concentration (MIC)* of that drug should be determined.

- A serial dilution of the selected drug is performed across a set of tubes or wells of a microtiter plate.
- A control tube containing no antibiotic is included to make certain that the organisms are still viable.
- A standard inoculum of bacteria is added to each tube, and all tubes are incubated.
- After a prescribed period of incubation, the tubes are observed for turbidity, reflecting a visible increase in bacterial numbers.
- The most dilute amount of drug in which there was no bacterial growth is defined as the MIC.



▲ **Figure 2-6.2** Determination of the Minimal Inhibitory and Minimal Bactericidal Concentrations

6.3 Minimal Bactericidal Concentration (MBC)

To determine the bactericidal activity of the drug, a sub-plating technique from the MIC called the *minimal bactericidal concentration (MBC)* is used.

- A small volume of liquid from the MIC tubes showing no visible growth is sub-plated onto large amounts of agar.
- This dilutes the antibiotic until it is no longer effective, freeing any organisms not killed at the MIC to create colonies.
- The MBC is defined as the concentration of drug at which no subsequent colonial growth occurs once the drug presence is removed.
- The MBC can be equal to or a higher concentration of drug than the MIC. It can never be a lower concentration.

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6.4 Clinical Infection Control

The three main forms of clinical infection control are:

1. **Sterilization:** Defined as the complete killing or removal of any viable agent. It is an absolute term, and no microbial agent can withstand a sterilizing treatment.
2. **Disinfection:** Not an absolute term. It refers to the removal of pathogens from an area, and when disinfectants are used on the skin, they are called *antiseptics*.
3. **Pasteurization (rapid heating and cooling of a liquid):** Developed for the beer and wine industries, this term is now most frequently used to refer to the removal of pathogens from milk. It is not a sterilizing treatment.

6.4.1 Physical Control Techniques

- **Autoclave:** 15 lbs. pressure, 121°C, 15–20 minutes (steam under pressure), sterilizes
- **Dry heat:** 180°C for 2 hours
- **Radiation:** Forms thymine dimers in DNA
- **Filtration:**
  - High Efficiency Particulate Air (HEPA)
  - Nitrocellulose
    - 0.45 μm filter: Removes all bacteria except those lacking cell walls
    - 0.22 μm filter: Removes all bacteria and spores

6.4.2 Chemical Control Techniques

- **Nucleic Acid Targeting Agents**
  - Malachite green
  - Crystal violet
- **Protein Denaturing Agents**
  - Formaldehyde
  - Glutaraldehyde
  - Ethylene oxide
  - Heavy metals
  - Hydrogen peroxide
  - Iodine
  - Chlorine
- **Membrane Damaging Agents**
  - Alcohol
  - Phenol
  - Detergents

- *Enveloped viruses* surrounded with a membrane captured from host cells are easily inactivated with membrane-damaging agents.
- *Naked capsid viruses* with a dense protein shell usually require a protein-denaturing agent to inactivate them.

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Chapters 1–2 Review Questions

1. A 28-year-old Peace Corps volunteer in Haiti suddenly develops fever, abdominal cramping, and voluminous, watery diarrhea. On physical exam she is tachycardic and has dry mucous membranes, decreased skin turgor, sunken eyes, and flat veins. Which of the following describes the mechanism of action of the toxin of the most likely causal bacterium?

A. ADP ribosylation of GTP binding protein
B. ADP ribosylation of Gi
C. ADP ribosylation of eukaryotic EF2
D. Inactivation of the host 60S ribosomal subunit
E. Increase of intracellular cGMP

2. A one-year-old boy is brought to the emergency department because of a runny nose, low-grade fever, and a cough that is becoming increasingly more violent. He now appears cyanotic and his coughs are followed with inspiratory stridor. His parents confess that he is not up to date on his vaccinations because they do not have access to medical care. Which of the following best describes the mechanism of action of the toxin produced by the most likely causal agent?

A. ADP ribosylation of GTP binding protein
B. ADP ribosylation of Gi
C. ADP ribosylation of eukaryotic EF2
D. Inactivation of the host 60S ribosomal subunit
E. Increase of intracellular cGMP

3. A 60-year-old male has been in the hospital recovering from coronary artery bypass surgery. The day after his Foley catheter is removed, he begins to complain of dysuria, frequency, and urgency. Urine analysis reveals elevated leukocytes and numerous gram-negative rods. Which of the following is the most important pathogenic mechanism of the most likely causal agent?

A. Biofilm
B. Capsule
C. Endotoxin
D. Exotoxin
E. Pili

4. An 80-year-old female is being treated for a fractured hip when she develops a fever and elevated WBC count. Blood and urine cultures are sent and she is started on empiric antibiotics. A chest x-ray is also obtained, which is clear. She quickly becomes tachycardic, hypotensive, anuric, tachypneic, and confused. Blood and urine cultures return positive for *E. coli*. Which of the following is most directly involved in the patient's hypotension?

A. Bacterial lipopolysaccharide
B. Interleukin-1
C. Mast cell degranulation
D. Nitric oxide
E. Tumor necrosis factor

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Review Questions Chapters 1–2

5. A 20-year-old college student was seen at the student health clinic with complaints of vaginal irritation and discharge. Speculum examination of the introitus revealed patchy erythema and thick white discharge. Gram-stained smear of the discharge showed gram-negative bacilli and gram-negative diplococci. She said she had unprotected sexual activity. What is the significance of the Gram-stain smear in this case?

A. It demonstrates laboratory contamination
B. It is evidence of infection with *Escherichia coli* and *Neisseria gonorrhoeae*
C. It is not useful as it is not possible to make a diagnosis this way
D. It provides a rapid diagnosis of infection
E. It strongly suggests gonococcal infection

6. A culture of smooth (encapsulated) *Streptococcus pneumoniae* is incubated until it reaches the stationary phase of the growth curve. The culture is then centrifuged to pellet the bacteria and the cell-free culture liquid is added to a culture of rough (non-encapsulated) organisms. Within two days, 35% of the rough colonies have become smooth. Which process most likely explains this event?

A. $F^+ \times F^-$ conjugation
B. Hfr $\times$ F^- conjugation
C. Generalized transduction
D. Specialized transduction
E. Transformation

7. Which of the following mechanisms is the most likely means by which normal flora diphtheroids can acquire the ability to cause pseudomembranous pharyngitis?

A. Transformation with acquisition of the toxin gene
B. $F^+ \times F^-$ conjugation
C. Phage conversion resulting in toxin production
D. Hfr $\times$ F^- conjugation
E. Vaccination resulting in pathogenic conversion

8. A nursing home resident requires hip replacement surgery after a fall. While receiving a course of post-operative antibiotics, she develops diarrhea. Which of the following treatments for bedpans should be implemented to destroy the most likely causal agent of her diarrhea?

A. Alcohol
B. Chlorox
C. Formaldehyde
D. Steam under pressure
E. Ultraviolet light

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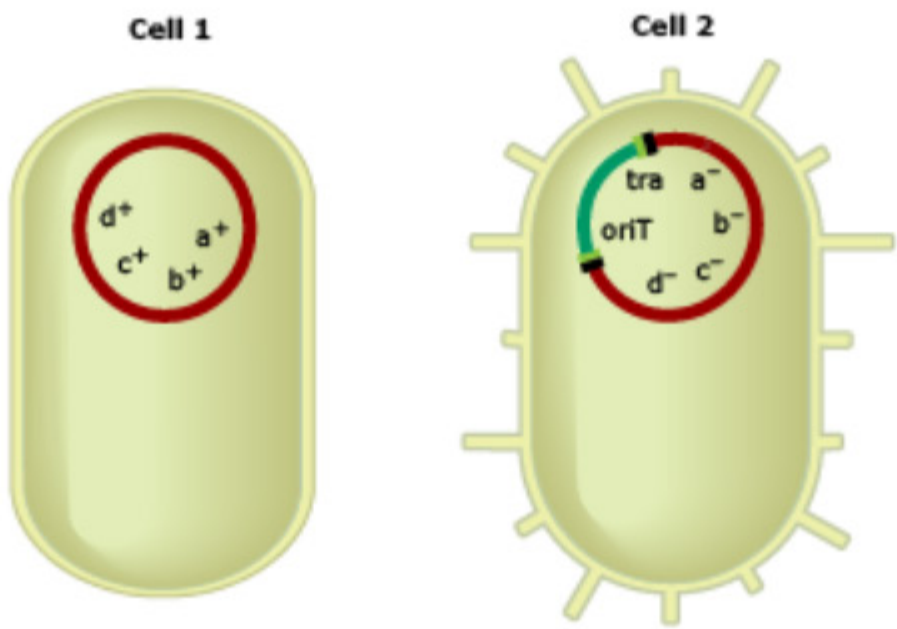
Chapters 1–2 Review Questions

9. A strain of methicillin-sensitive *Staphylococcus aureus* becomes methicillin-resistant after culture with a single methicillin-resistant organism. Which of the following is the correct combination of circumstances most likely to have occurred in this case?

	Resistance Gene Location	Transfer Vector	Process
A.	Chromosome	Free DNA	Transformation
B.	Chromosome	F^+ donor	Conjugation
C.	Chromosome	Hfr donor	Conjugation
D.	Chromosome	Phage	Transduction
E.	Plasmid	Free DNA	Transformation
F.	Plasmid	F^+ donor	Conjugation
G.	Plasmid	Hfr donor	Conjugation
H.	Plasmid	Phage	Transduction

10. If cell 1 and cell 2 from the figure below were mixed in culture, what would be the most likely outcome?



A. Both cells would be male in phenotype
B. Cell 1 would acquire the a^- allele
C. Cell 1 would acquire the d^- allele
D. Cell 2 would acquire the a^+ allele
E. Cell 2 would acquire the d^+ allele

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Review Answers Chapters 1–2

1. The correct answer is A. This profoundly dehydrated patient has cholera. The cholera toxin acts by ADP ribosylating GTP binding protein, leaving Gs locked on, which precipitates an increase in intracellular cAMP and resultant fluid and electrolyte loss in the form of a watery diarrhea.

2. The correct answer is B. This child has whooping cough caused by *Bordetella pertussis*. The pertussis toxin ADP ribosylates Gi, the negative regulator of adenylate cyclase. This results in increased intracellular cAMP and fluid loss manifested as edema in the tissues.

3. The correct answer is E. *Escherichia coli* is the most common cause of urinary tract infection, and in the absence of any culture indications to the contrary, should be assumed to be the cause of this patient's condition. The most important pathogenic attribute for the urotropic *E. coli* strains is their ability to adhere to the uroepithelium by some form of pili.

4. The correct answer is D. This is endotoxin shock, but the direct cause of hypotension in this case is the production of nitric oxide, which causes the dilation and leakage of vessels and precipitates the decline in blood pressure. Other factors which contribute to this are IL-6, IL-8, platelet activating factor, and reactive oxygen species.

5. The correct answer is C. This is a question about normal flora. Regardless of the symptoms and signs and suggestions made by the case history, the Gram stain alone is not sufficient to make the diagnosis of gonorrhoea in the female. In the male, there is no confounding normal flora, so Gram stain of an urethral exudate containing gram-negative diplococci is indeed diagnostic. In the female, however, normal flora of the genus *Veillonella* are gram-negative diplococci, so the diagnostic next step is culture on Thayer-Martin selective medium or DNA probe.

6. The correct answer is E. The only genetic exchange process of bacteria that is possible with cell-free liquids is transformation. This is a common process with *Streptococcus pneumoniae* since it is competent to take up free DNA from its environment during a large portion of its life cycle.

7. The correct answer is C. Normal flora diphtheroids can be converted to pathogenic *Corynebacterium diphtheriae* by infection with the β-corynephage. This is an example of lysogenic conversion, where a temperate phage integrates its genome into the bacterial chromosome and thereby imparts new genetic traits to the bacterium.

8. The correct answer is D. This patient has most likely developed *Clostridium difficile* pseudomembranous colitis as a result of her antibacterial regimen. Since *Clostridium* is a spore-forming gram-positive rod, the question really becomes what treatment will destroy bacterial spores. The only sterilizing technique on the list is the autoclave, correctly described as the application of steam under pressure. Chemical disinfectants are not generally effective at killing bacterial spores.

9. The correct answer is D. The gene that confers methicillin resistance is a chromosomal gene that encodes an altered penicillin-binding protein. It is transferred between *Staphylococcus aureus* organisms by phages, in the process known as transduction.

10. The correct answer is C. Cell 1 is an F- cell, phenotypically a recipient in this conjugal cross. Cell 2 is an Hfr cell, the donor of chromosomal genes in this setting. The genetic exchange will therefore go from cell 2 to cell 1, and the gene most likely to be transferred is that closest to oriT, which is d-.

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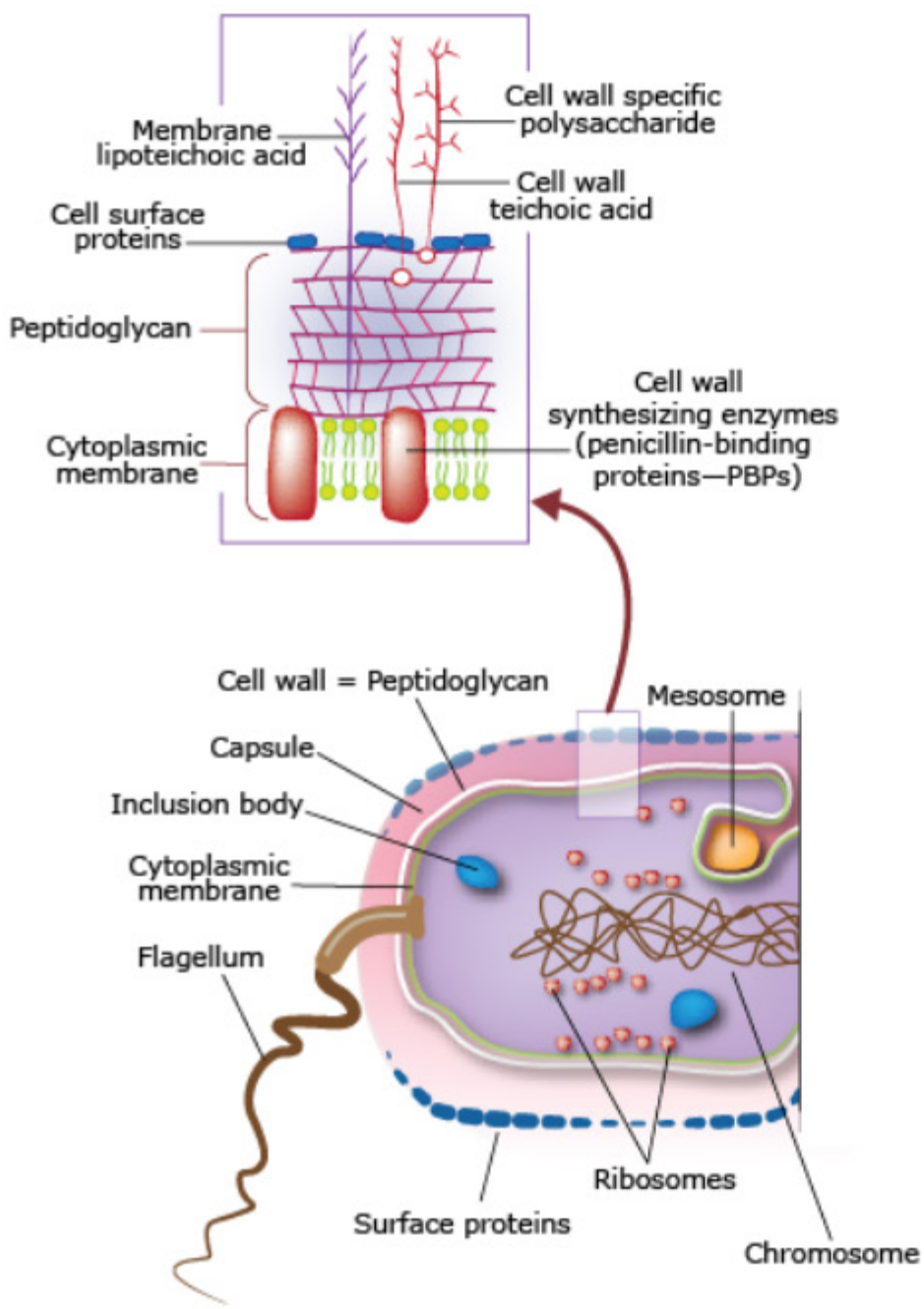
1 Structure and Morphology

1.1 Bacterial Cell Envelope

Bacteria are divided into two major anatomical groups depending on their response to the Gram stain. The most important differences between these two groups of organisms are:

- Gram-negative bacteria possess an *outer membrane* that contains *endotoxin*.
- Gram-positive bacteria have *thicker cell walls* than gram-negatives.
- Gram-positive bacteria have *teichoic acids* on their surfaces.



▲ **Figure 3-1.1A** Gram-Positive Cell Envelope

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the anatomy and physiology of the major categories of prokaryotes.
- Distinguish the major types of bacterial disease.
- Identify the causal agent from symptomatic, diagnostic, and epidemiologic clues.
- Answer basic science questions about the agent concerning anatomy, physiology, and pathogenesis.

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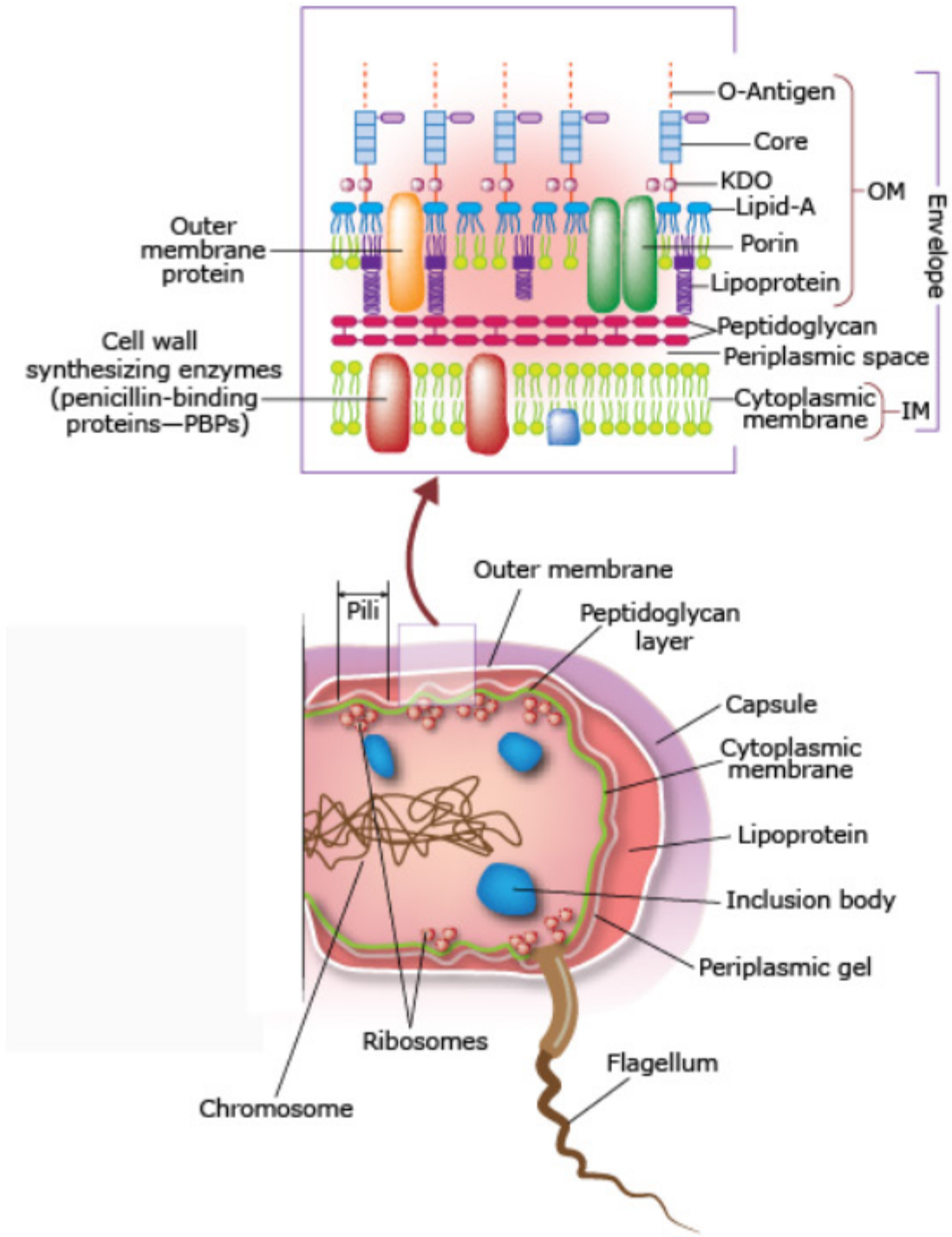
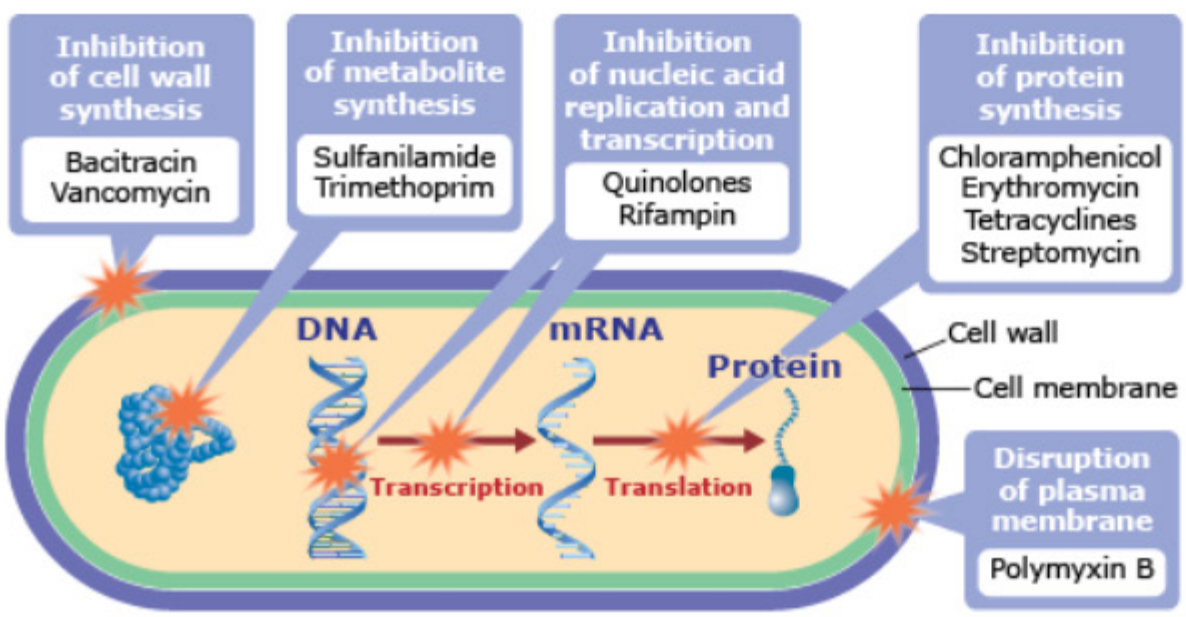


▲ **Figure 3-1.1B** Gram-Negative Cell Envelope



▲ **Figure 3-1.1C** Location of Antibacterial Action

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▼Table 3–1.1 Bacterial Structure and Morphology

Structure	Presence	Composition	Function
Capsule (slime layer, glycocalyx)	Many gram+ and gram−	Polysaccharide gel except *Bacillus anthracis* = poly D-glutamate	Protects from phagocytosis, immunogenic except *Streptococcus pyogenes* (hyaluronic acid) and type b *Neisseria meningitidis* (sialic acid)
Outer membrane	*Only gram−*	*Lipopolysaccharide = endotoxin*	Hydrophobic membrane, *Lipid A = toxic*, polysaccharide = weakly immunogenic
		Outer-membrane proteins	Adherence, antigenic variation
		Porin proteins	Passive transport
Cell wall	Thick in gram+, thin in gram−	*Peptidoglycan*, mesh of N-acetylglucosamine and N-acetylmuramic acid	Rigid support, shape, protection from osmotic damage; synthesis *inhibited by penicillins and cephalosporins*, responsible for Gram stain reaction
	Gram+ only	Teichoic acids	Adherence, immunogenic, induce IL-1, TNF-α
	Acid-fast only	Mycolic acids	Staining characteristics, resistance to desiccation and chemicals
Periplasmic space	Gram− only	Space between two membranes	Regulates osmotic pressure, enzymes may accumulate here
Cytoplasmic (inner, plasma) membrane	Both gram+ and gram−	Phospholipid bilayer	Selective permeability, active transport, site of any biochemical process which requires membrane support
		Penicillin-binding proteins (PBPs) = transpeptidases and carboxypeptidases	Enzymes which synthesize the cross-linkages in peptidoglycan. Penicillin and cephalosporins bind and inactivate

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1.2 Bacterial Spore Formation

1.2.1 Organisms

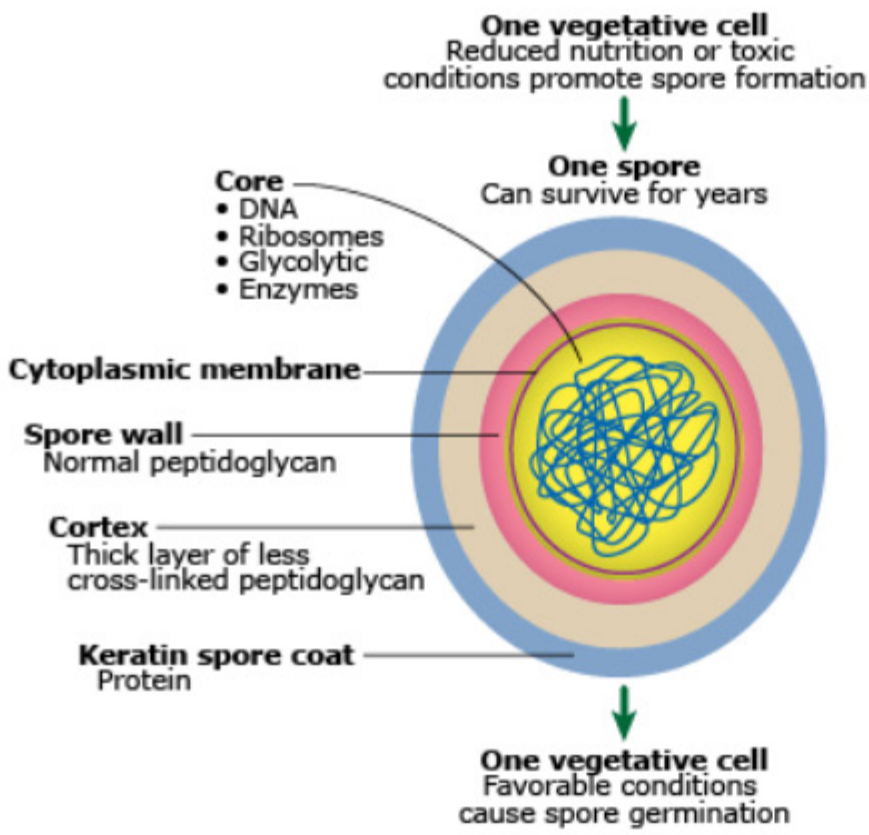
- *Bacillus*
- *Clostridium*

1.2.2 Function

- Survival; resistance to heat, desiccation and toxic materials
- Not reproductive

1.2.3 Resistance Mechanisms

- Thick coat of keratin and peptidoglycan
- New enzymes: *calcium dipicolinate* and *dipicolinic acid synthetase*, heat-resistant catalase



▲ **Figure 3-1.2** Endospore

Fungi use their spores for reproduction as well as for survival and dissemination.

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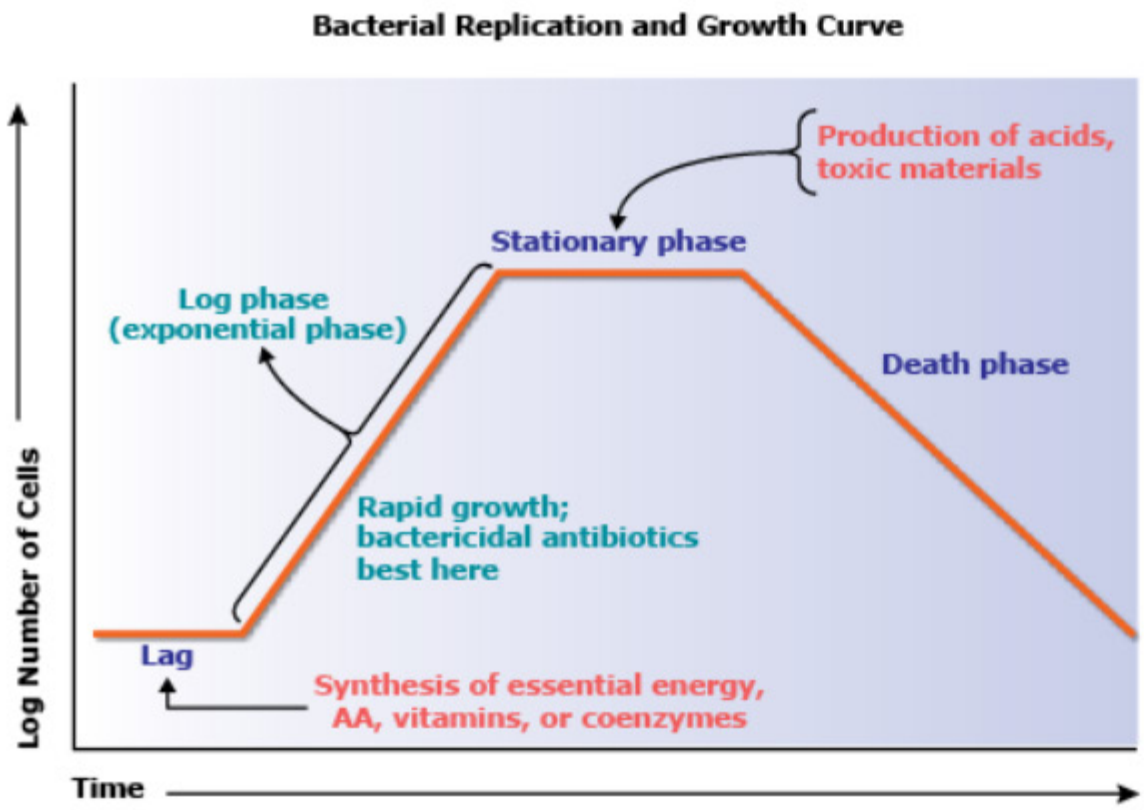
2 Physiology

2.1 Bacterial Replication and Growth

Bacteria divide by binary fission, so their exponential growth occurs by factors of two. When bacteria are dropped into a new culture vessel, they will go through four phases of growth which have no analogy to the eukaryotic cell cycle.



▲ **Figure 3-2.1** Four Phases of Bacterial Growth

▼ **Table 3–2.1** Special Bacterial Growth Requirements

Nutritional Requirement	Organism
Cholesterol, purines, and pyrimidines	*Mycoplasma*
Cysteine	*Francisella, Brucella, Legionella,* and *Pasteurella;* but not *Bordetella*
X (protoporphyrin) and V (NAD)	*Haemophilus*

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2.2 Oxygen Utilization

Bacteria are classified according to their oxygen utilization and their possession of two important enzymes:

$$O_2\bullet^- + 2H^+ \xrightarrow{\text{superoxide dismutase}} H_2O_2 + \xrightarrow{\text{catalase}} H_2O + \tfrac{1}{2}O_2$$

▼ **Table 3–2.2** Bacterial Oxygen Requirements

Classification	Characteristics	Important Examples
Obligate aerobes	• Require oxygen • Have no fermentation pathways • Generally produce superoxide dismutase	*Mycobacterium* *Pseudomonas* *Bacillus* *Nocardia* *Corynebacterium*
Microaerophiles	Require low but not full oxygen tension (~5%)	*Campylobacter* *Helicobacter*
Facultative anaerobes	Will respire aerobically until oxygen is depleted and then ferment	Most bacteria; e.g., *Enterobacteriaceae*
Obligate anaerobes	• Killed by oxygen • Lack superoxide dismutase • Generally lack catalase • Are fermenters • Cannot use oxygen as terminal electron acceptor	*Actinomyces* *Bacteroides* *Clostridium*

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3 Laboratory Techniques

3.1 Bacterial Culture Media

3.1.1 General Principles

- **Tissue/Cell Culture:** Required for *obligate intracellular* organisms.
- **Inert Agars or Broths:** Suitable for extracellular or facultative intracellular organisms.
  - **Selective Media:** Select for the growth of organisms by including special nutrients or inhibiting normal flora.
  - **Differential Media:** Allow multiple organisms to grow but allow differentiation on the basis of colonial color or morphology.

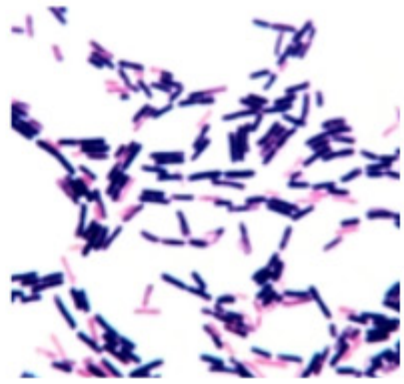
▼ **Table 3–3.1A** Commonly Tested Media

Organism	Medium
Corynebacterium	Loeffler's coagulated serum medium *Tellurite agar:* dark gray/black colonies
Enteric bacteria	Eosin methylene blue (EMB) MacConkey agar: lactose fermenters vs. lactose nonfermenters
Intestinal pathogens	Hektoen enteric agar Xylose-lysine-deoxycholate agar
Legionella	*Charcoal-yeast extract agar* (CYE agar): contains cysteine and iron
Mycobacterium	Lowenstein-Jensen medium: contains egg yolk and antibiotics to suppress non-mycobacterial growth
Neisseria from normally sterile sites, *Haemophilus*	*Chocolate agar*
Neisseria from sites with normal flora	*Thayer-Martin medium:* contains vancomycin, colistin, and nystatin to inhibit normal flora
Vibrio cholerae	*Thiosulfate citrate bile salts sucrose* (TCBS): extremely alkaline
Anaerobes	*Thioglycolate*

3.1.2 Stains

Gram Stain This stain is the foundation of microbiological diagnosis. Some summary statements:

- *All cocci are gram-positive* except *Neisseria, Moraxella*, and *Veillonella*.
- *All spore formers are gram-positive*.
- Any modification of the technique for use with tissues will cause human cells to stain pink.



Dr. Jack Bostrack/Visuals Unlimited, Inc.

▲ **Figure 3-3.1A** Gram-Positive and Gram-Negative Bacilli

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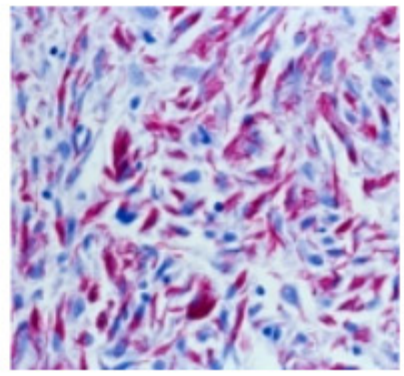
▼ **Table 3–3.1B** Gram Stain

Procedure	Gram-Positive	Gram-Negative
Primary stain, *crystal violet*, tiny intense purple molecule	Blue/purple	Blue/purple
Gram's iodine (complexing agent, binds primary stain to larger molecules)	Large purple complex	Large purple complex
Wash (*acetone/alcohol*)	Blue/purple	Colorless
Counterstain, *safranin*, pale pink	Blue/purple	Pink

Acid-Fast Stain (Ziehl-Neelsen or Kinyoun) This stain is used for organisms with extremely waxy cell envelopes. The function of the test depends on the organisms being heated to melt the wax or being shocked by a change in pH.

- *Mycobacterium will be acid-fast*.
- *Nocardia is partially acid-fast*.
- Human cells will stain blue.



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▲ **Figure 3-3.1B** Acid-Fast Bacilli

▼ **Table 3–3.1C** Acid-Fast Stain

Procedure	Acid-Fast	Non Acid-Fast
Carbol fuchsin with heat or pH change	Bright red	Bright red
Acid alcohol (wash)	Red	Colorless
Methylene blue	Red	Blue

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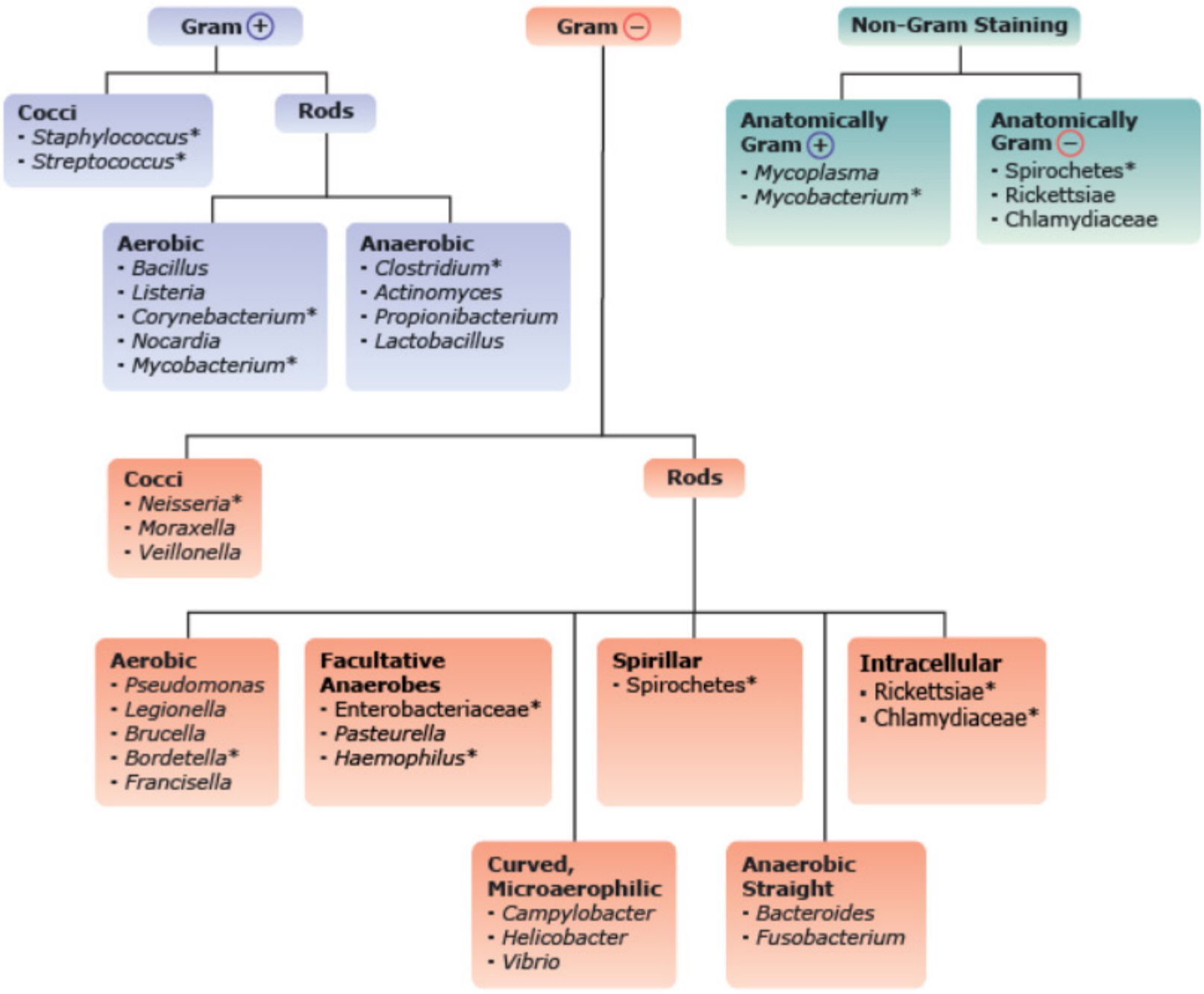
4 Overview of the Medically Important Bacteria



*Organisms that are likely to get multiple questions on Step 1 exam.

▲ **Figure 3-4.0** Bacterial Taxonomy

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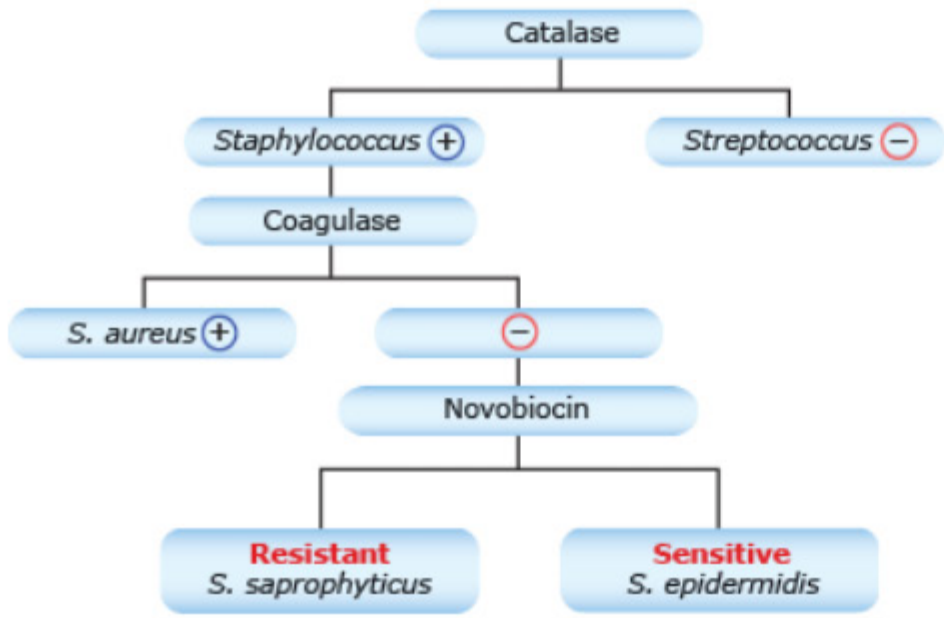
5 Gram-Positive Cocci



▲ **Figure 3-5.0** Laboratory Algorithm: Gram-Positive Cocci

5.1 *Staphylococcus*

5.1.1 Genus Characteristics

- Gram-positive cocci
- Grape-like clusters
- Catalase positive

5.1.2 *Staphylococcus aureus*

Species Characteristics

- *Coagulase positive*
- *Golden colonies* on blood agar
- *β-hemolytic*
- Ferments mannitol on *mannitol salt agar*

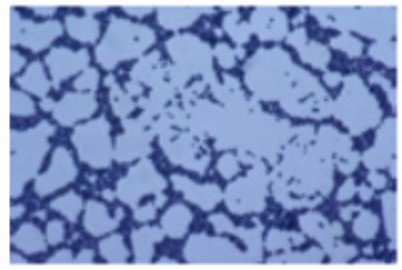
Reservoir Normal flora, nose and skin

Transmission

- Hands
- Sneezing
- Surgical wounds
- Contaminated food

Predisposing Factors

- Breaks in skin
- Foreign body
- Neutropenia
- Intravenous drug abuse
- Chronic granulomatous disease
- Cystic fibrosis


Michael Abbey/Science Source

▲ **Figure 3-5.1** Gram-Positive Cocci in Clusters: *Staphylococcus*

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Pathogenic Features

- **Coagulase:** Converts fibrinogen to fibrin
- **Alpha Toxin:** Pore-forming, cytolytic toxin
- **Protein A:** Inhibits IgG opsonization by binding Fc component
- **Enterotoxins:** Fast acting, heat stable
- **Toxic Shock Syndrome Toxin-1 (TSST-1):** Acts as superantigen
- **Exfoliatins:** Proteases specific for cadherin desmoglein 1, promote epidermal blistering of scalded skin syndrome and bullous impetigo

▼ **Table 3–5.1** Clinical Syndromes of *S. aureus*

Presentation	Key Vignette Clues	Pathogenesis
Food poisoning	*3–6 hours onset, salty foods, picnics* (ham, canned meats, custard pastries, potato salad)	Enterotoxins A-E, preformed in food, heat stable
Infective endocarditis	*Acute* onset, fever, malaise, leukocytosis, heart murmur	Coagulase, cytolytic toxins
Pneumonia	*Typical pneumonia, salmon-colored sputum*, nosocomial, ventilator, postinfluenza, high fatality	Coagulase, cytolytic toxins
Osteomyelitis (No. 1 cause overall)	Bone pain, fever, swelling, redness, lytic lesions on imaging	Coagulase, cytolytic toxins
Surgical infections	Fever, cellulitis, abscess	Coagulase, exfoliatins, TSST
Mastitis	Subcutaneous tenderness, swelling, heat, redness	Coagulase, cytolysins
Impetigo	Erythematous papules and bullae	Coagulase, exfoliatins
Scalded skin syndrome	Diffuse epidermal peeling	Coagulase, exfoliatins
Toxic shock syndrome	Scarlatiniform rash desquamates, *involves palms and soles*, fever, hypotension, multiorgan failure	TSST-1 (*superantigen*)

Treatment

- Gastroenteritis: Self-limiting
- Nafcillin/oxacillin
- Methicillin-resistant *Staphylococcus aureus* (MRSA): Vancomycin
- Vancomycin-resistant (VRSA) or vancomycin-intermediate (VISA): Quinupristin/dalfopristin

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5.1.3 *Staphylococcus epidermidis*

Species Characteristics

- *Coagulase-negative Staphylococcus*
- Gamma hemolytic
- *Novobiocin sensitive*

Pathogenic Features

- *Biofilm* production
- Normal flora of skin

Clinical Syndromes

- Subacute endocarditis in IV drug users
- Infections of catheters and prosthetic devices

Treatment Vancomycin with rifampin or an aminoglycoside

5.1.4 *Staphylococcus saprophyticus*

Species Characteristics

- *Coagulase-negative Staphylococcus*
- Gamma hemolytic
- *Novobiocin resistant*

Clinical Syndromes "Honeymoon cystitis"

Treatment Quinolones

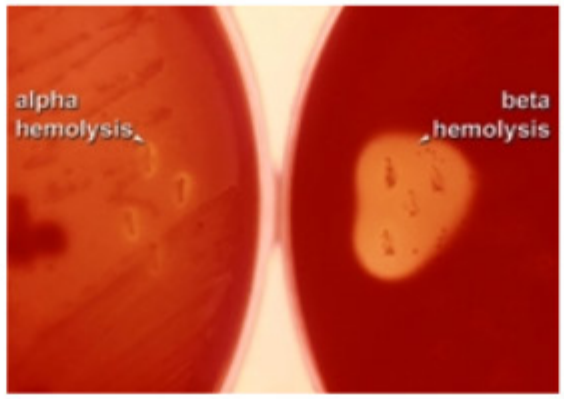
5.2 *Streptococcus*

5.2.1 Genus Characteristics

- Gram-positive cocci
- Chains or pairs
- Catalase negative

Michael Abbey/Science Source

▲ **Figure 3-5.2A** Gram-Positive Cocci in Chains



CDC/Richard R. Facklam, PhD

▲ **Figure 3-5.2B** Patterns of Hemolysis

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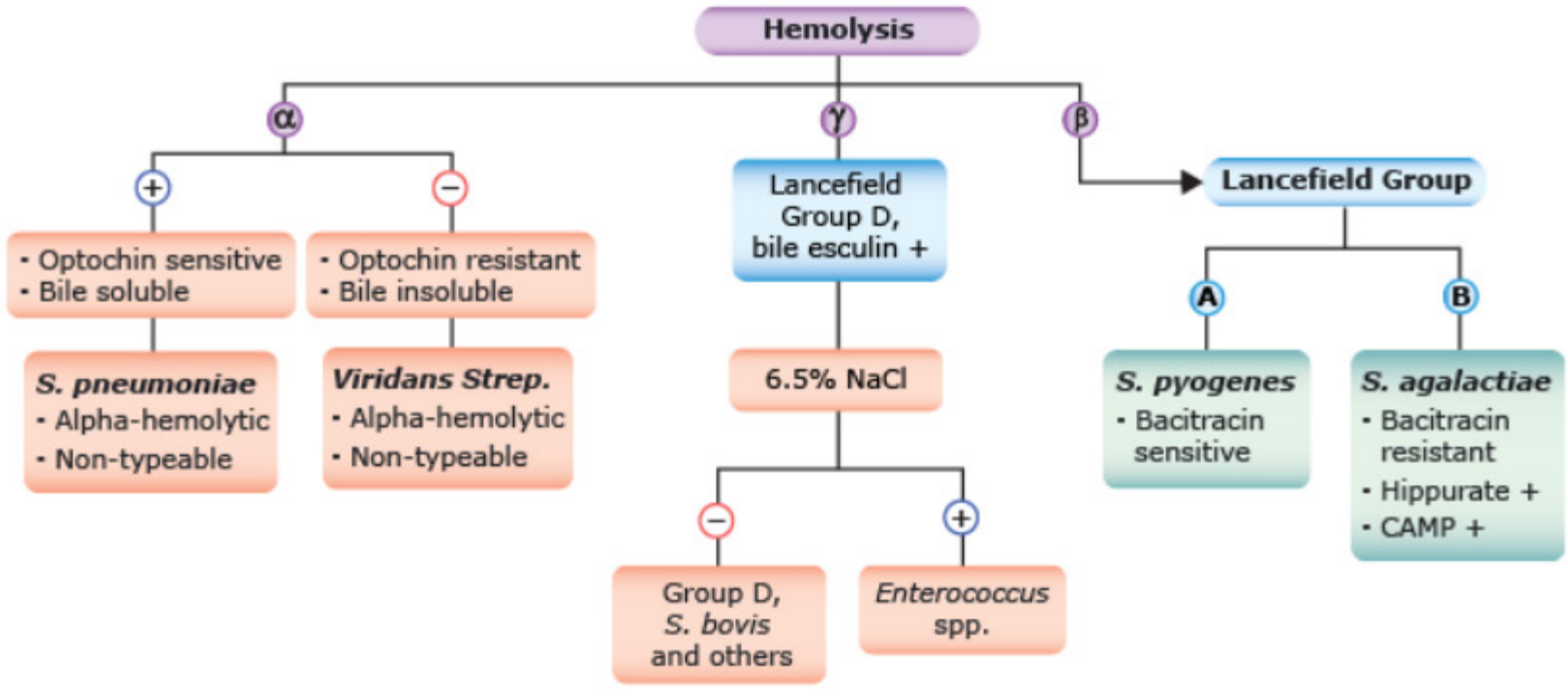
5.2.2 Further Classification

The genus *Streptococcus* is divided into groups by classification of a *cell wall carbohydrate (C carbohydrate)*. Analysis with this technique separates four medically important groups: A, B, D, and those that are "ungroupable" because they lack this carbohydrate. In clinical microbiology, we distinguish the streptococci on the basis of their patterns of hemolysis and associate that result with our knowledge of the four Lancefield groups.



▲ **Figure 3-5.2C** Laboratory Algorithm: *Streptococcus*

5.2.3 β-Hemolytic Streptococci

Group A *Streptococcus* (GAS; *Streptococcus pyogenes*)

Species Characteristics

- β-hemolytic
- Bacitracin sensitive
- Pyrrolidonyl arylamidase (PYR) positive

Reservoir Throat and skin

Transmission Respiratory droplets, direct contact

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▼Table 3–5.2A Pathogenic Features of *S. pyogenes*

Category of Action	Product	Mechanism of Pathogenesis
Surface features	Pili and teichoic acids	Attachment
	Hyaluronic acid capsule	Anti-phagocytic and nonimmunogenic
	M protein	Binds serum Factor H, *destroys C3 convertase*, and prevents C3b opsonization; used for serotyping GAS
	F protein	*Fibronectin-binding protein* mediates adherence
Soluble secretions	Exotoxins A–C	*Erythrogenic, pyrogenic*, cause fever and rash of scarlet fever, produced by lysogeny, act as *superantigens*
	Streptolysin O	Oxygen-labile hemolytic exotoxin which shares epitopes with *myosin* in heart and collagen in joints
	Streptolysin S	Oxygen stable, hemolytic exotoxin with *leukocidin* activity
	C5a peptidase	*Inactivates C5a anaphylatoxin* and impedes neutrophil chemotaxis
	Chemokine protease	*Degrades IL-8*, impedes neutrophil chemotaxis
Spreading factors	Streptokinase	*Breaks down fibrin* clot
	Streptodornase	*DNAse*, liquefies pus
	Hyaluronidase	Degrades hyaluronic acid, allows spread through extracellular matrix

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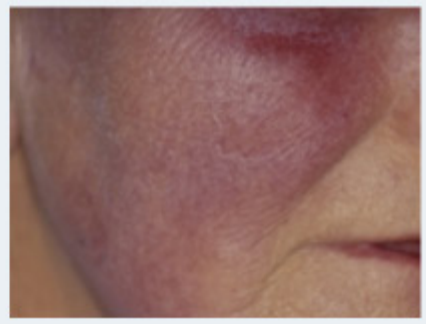
Clinical Syndromes

▼Table 3–5.2B Acute Suppurative Infections of *S. pyogenes*

Disease	Symptoms/Diagnosis	Pathogenesis
Pharyngitis	Abrupt onset of headache, fever, sore throat, abscesses on tonsillar pillars, tender cervical lymphadenopathy; rapid strep EIA test misses 25%, *culture all negatives on blood agar with bacitracin disc*	Adherence factors and antiphagocytic factors
Scarlet fever	All of the above plus *blanching sandpaper rash* which spares palms and soles, circumoral pallor, *strawberry tongue*, nausea, and vomiting	All of the above *plus exotoxins A–C*
Impetigo/pyoderma	*Honey-crusted* lesions of skin	Adherence factors, antiphagocytic factors
Necrotizing fasciitis	Rapidly spreading tissue necrosis from point of initial wound	Adherence factors, antiphagocytic and spreading factors
Erysipelas	Cutaneous swelling with sharp border	Exotoxins from superficial infections 

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▼ **Table 3–5.2C** Non-suppurative Sequelae of *S. pyogenes*

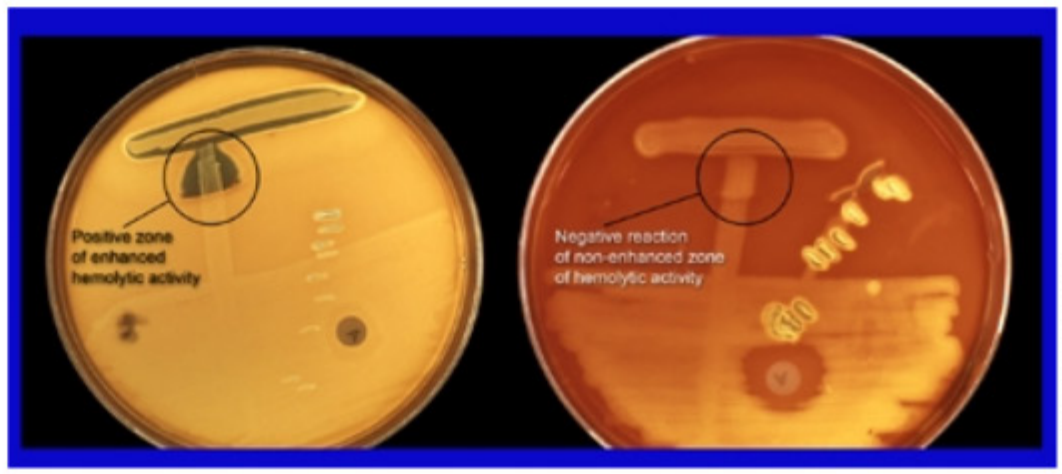
Disease	Follows	Symptoms/Diagnosis	Pathogenesis
Rheumatic fever	Pharyngeal infection with M types 1,3,5,6,18	6–15 years old, 3–4 weeks after pharyngitis presents with polyarthritis, carditis, erythema marginatum, fever, *ASO titer > 200*	*Type II hypersensitivity* due to molecular mimicry between GAS and myosin in heart and collagen in joints
Acute glomerulonephritis	Pharyngeal or cutaneous infection with *M12* and others	6–8 years old, 10 days post acute infection; edema, hematuria, proteinuria, hypertension	*Type III hypersensitivity*, immune complexes damage glomerular basement membrane

Treatment: β lactams or macrolides

Group B *Streptococcus* (GBS; *Streptococcus agalactiae*)

Species Characteristics

- β-hemolytic
- Bacitracin resistant
- Hydrolyses hippurate
- CAMP test positive (detects an incomplete hemolytic polypeptide which works with the sphingomyelinase of *Staphylococcus aureus* to produce enhanced hemolysis)



CDC/Dr. Richard Facklam

▲ **Figure 3-5.2 D** CAMP Test: Positive for GBS (*left*) and Negative for GBS (*right*)

Reservoir Vaginal flora of 15% to 20% of women

Transmission To the neonate during parturition, especially during difficult, prolonged labors

Pathogenic Features

- Capsule
- β hemolysin
- CAMP factor

Clinical Syndromes/Diagnosis

- *Neonatal meningitis and septicemia, No. 1 cause*
- Diagnosis by Gram stain of CSF

Treatment Ampicillin with aminoglycoside or cephalosporin

Prophylaxis

- Ampicillin or penicillin during delivery for women with positive cultures or recent history of infection
- Clindamycin or erythromycin if allergies exist

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5.2.4 α-Hemolytic Streptococci

Streptococcus pneumoniae

Species Characteristics

- Lancet-shaped diplococcus
- α-hemolytic
- Optochin sensitive
- Lysed by bile

Reservoir Upper respiratory tract

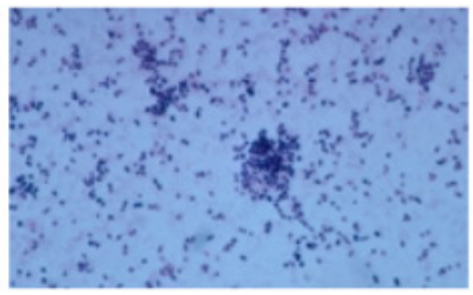
Transmission Respiratory droplets

Predisposing Factors

- Damage to lung's natural cleansing mechanisms
  - Antecedent influenza (damage to mucociliary escalator)
  - COPD
  - Congestive heart failure
  - Alcoholism (loss of gag reflex)
- *Asplenia*: Predisposes to any encapsulated organism spreading via the blood

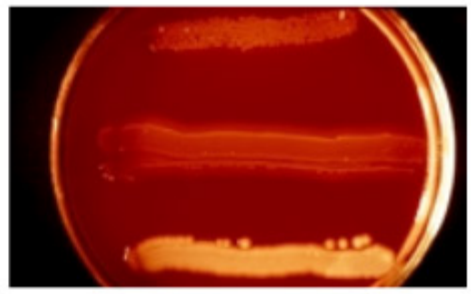
Pathogenic Features

- Capsule
- IgA protease
- Teichoic acids
- Pneumolysin O: Released with bacterial death; damages respiratory epithelium, inhibits respiratory burst, and inhibits complement fixation



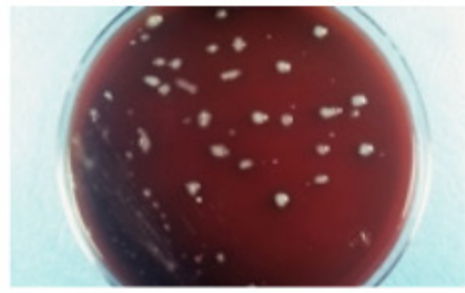
Michael Abbey/Science Source

▲ **Figure 3-5.2E** Lancet-Shaped Diplococcus: Pneumococcus



Michael Gabridge/Custom Medical Stock Photo

▲ **Figure 3-5.2F** Alpha Hemolysis (Middle Streak)



Raymond Otero/Visuals Unlimited, Inc.

▲ **Figure 3-5.2G** Mucoid Colonies: Encapsulated

▼ **Table 3–5.2D** Clinical Syndromes/Diagnosis/Treatment of *S. pneumoniae*

Disease Syndrome	Symptoms/Diagnosis	Treatment
Typical pneumonia (No. 1 cause)	Fever, chills, lobar consolidation, *rusty sputum*	Macrolides
Adult meningitis (No. 1 cause)	*CSF with high PMNs, low glucose, high protein, gram-positive diplococci*, Quellung reaction or latex particle agglutination to serotype capsular antigens	Ceftriaxone or cefotaxime
Otitis media and sinusitis (No. 1 cause)	Red, bulging tympanic membrane, fever, pain	Amoxicillin; erythromycin if allergic

Courtesy of the Centers for Disease Control

Prophylaxis

- **Pediatric Vaccine:** PCV, pneumococcal conjugate vaccine; 13 of the most common capsular serotypes conjugated to diphtheria toxoid
- **Adult Vaccine:** PPV, pneumococcal polysaccharide vaccine; 23 of the most common capsular serotypes; recommended for all adults >65, those who are immunocompromised, and asplenics

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Viridans Group Streptococci (*S. mutans, S. sanguis, S. interrogans,* and others)

Species Characteristics

- α-hemolytic
- Optochin resistant
- Insoluble in bile

Reservoir Oropharynx

Transmission Endogenous

Pathogenic Features Dextran-mediated biofilm

Clinical Syndromes

- Plaque and dental caries
- *Subacute endocarditis* in patients with dental work or preexisting damage to heart valves

Treatment Penicillin G with aminoglycosides for endocarditis

Prophylaxis Antibiotics prior to dental work in any patient with damaged heart valves

5.2.5 Group D Streptococci (*Enterococcus, Streptococcus bovis*)

Species Characteristics

- Variable hemolysis, usually gamma
- PYR test positive
- Hydrolyze esculin in 40% bile and 6.5% NaCl

Reservoir Colon, urogenital tract

Transmission Endogenous

B. Slaven MD/Custom Medical Stock Photo

▲ **Figure 3-5.2H** Colon Cancer Lesion

Predisposing Factors

- Injuries (medical procedures, colon cancer lesions) to gastrointestinal or genitourinary tract allow entry into blood
- Preexisting damage to valves

Pathogenic Features Bile and salt tolerance promote survival in bowel and gall bladder

Clinical Syndromes

- Urinary and biliary tract infections
- Subacute endocarditis

Treatment

- All strains have some drug resistance
- Vancomycin-resistant strains have *D-alanyl-D-lactate terminal residue* in cell wall pentapeptide which will not bind the drug

Prophylaxis Penicillin and gentamicin before GI or GU surgery in patients with preexisting damage to heart valves

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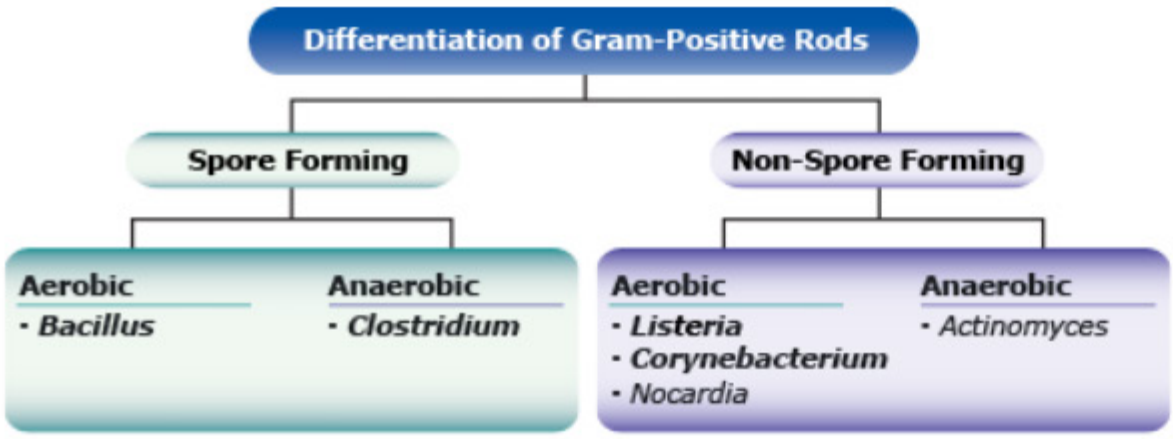
6 Gram-Positive Rods



▲ **Figure 3-6.0** Laboratory Algorithm Gram-Positive Rods

▼ **Table 3–6.0** Gram-Positive Rods

Genus	Spores	Anaerobic Growth	Motility	Exotoxins	Filaments	Facultative Intracellular Growth	Immuno-compromised Hosts	Acid Fast
Bacillus	*Yes*	No	Yes, except *B. anthracis*	*Yes*	No	No	No	No
Clostridium	*Yes*	*Yes*	Yes, except *C. perfringens*	*Yes*	No	No	No	No
Corynebacterium	No	No	No	*Yes*	No	No	No	No
Listeria	No	No	Yes, *tumbling* motility	No	No	*Yes*	*Yes*	No
Actinomyces	No	*Yes*	No	No	*Yes*	No	No	No
Nocardia	No	No	No	No	*Yes*	No	*Yes*	*Partially*
Mycobacterium	No	No	No	No	No	*Yes*	*Yes*	*Yes*

6.1 Spore Formers

6.1.1 *Bacillus*

Genus Characteristics

- Gram-positive bacilli
- Aerobic
- Spore forming

Bacillus anthracis

Species Characteristics

- Large, boxcar shaped

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- Spore forms within rod (bamboo appearance)
- *Poly-D-glutamate capsule*

Reservoir/Transmission

- Animal hides
- Soil
- Inhalation or implantation of spores

Pathogenic Factors

- **Anthrax Toxin** (three-component, heat-labile exotoxin):
  - **Edema Factor (EF):** Binds calmodulin and acts as adenylate cyclase
  - **Lethal Factor (LF):** Kills cells
  - **Protective Antigen (PA):** Mediates entry of EF and LF; immunogenic, used in the vaccine
- **Capsule:** Anti-phagocytic

Clinical Syndromes

- **Cutaneous Anthrax:** Skin ulcer, "malignant pustule" or "black eschar"
- **Pulmonary Anthrax:** Rapidly fatal pneumonia, fever, malaise, nonproductive cough, *mediastinal widening*, hemorrhagic mediastinal lymphadenitis
- **Gastrointestinal Anthrax:** Very rare, vomiting, diarrhea, eventual bacteremia

Diagnosis

- Gram stain and culture of blood, sputum, lesion
- PCR
- Serology

Treatment

- Ciprofloxacin
- Doxycycline

Prevention Toxoid vaccine, used by military and high-risk individuals

Bacillus cereus

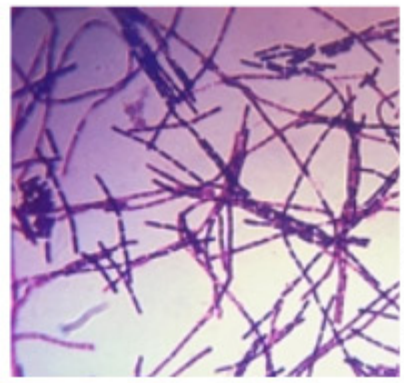
Clinical Syndromes Rapid onset (from 1 to 6 hours) food poisoning associated with buffet-style restaurants and rice dishes

Virulence Factors

- **Emetic Toxin:** Preformed, fast-acting (from 1 to 6 hours)
- **Diarrheal Toxin:** Produced in vivo, increases cAMP, slow acting (18 hours)

Diagnosis Clinical

Treatment Supportive

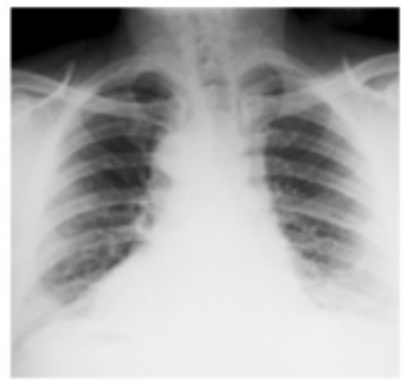


Courtesy of the Centers for Disease Control

▲ **Figure 3-6.1A**
Bacillus anthracis

Courtesy of the Centers for Disease Control

▲ **Figure 3-6.1B**
Anthrax Eschar



CDC/Arthur E. Kaye

▲ **Figure 3-6.1C**
Mediastinal Widening in Pulmonary Anthrax

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6.1.2 *Clostridium*

Genus Characteristics

- Gram-positive bacilli
- Spore forming *(terminal spores)*
- *Anaerobic*

Clostridium tetani

Reservoir/Transmission Soil, traumatic implantation

Pathogenic Features

- **Toxin:** *Tetanospasmin*
- Carried intra-axonally to CNS, where it blocks inhibitory neurotransmitters (glycine and GABA); excitatory neurons are unopposed leading to spastic (rigid) paralysis

Clinical Syndromes

- **Trismus:** Lock jaw
- **Risus Sardonicus:** Sardonic grin
- **Opisthotonus:** Unopposed contraction of back muscles

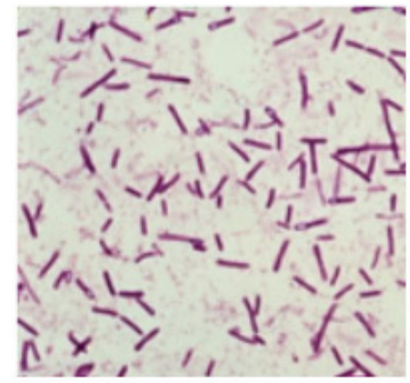
Courtesy of the Centers for Disease Control

▲ **Figure 3-6.1F** Opisthotonus

Wound Management

▼ **Table 3–6.1A** Tetanus Wound Management

Patient	Tetanus Prone	Not Tetanus Prone
Type of wound	Old, dirty, crushing injury	Fresh, clean, good blood perfusion
Completed primary series	Booster at 5-year intervals	Booster at 10-year intervals
Status unknown or uncompleted primary series	Tetanus immune globulin plus vaccine	Vaccinate



Michael Abbey/Science Source

▲ **Figure 3-6.1D** *Clostridium*

CDC/Dr. Thomas F. Sellers/Emory University

▲ **Figure 3-6.1E** Risus Sardonicus

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Treatment

- Hyperimmune human globulin (TIG) to neutralize toxin plus metronidazole or penicillin
- Spasmolytic drugs; debride; delay closure

Prophylaxis

- *Toxoid vaccine*, component of DTaP, repeated at 10-year intervals after primary series

Clostridium botulinum

Reservoir/Transmission Soil, dust/foodborne, traumatic implantation

Pathogenic Features

- *Botulinum toxin: Blocks acetylcholine release, flaccid paralysis*
- Heat labile at 60°C, absorbed by gut, carried by blood to peripheral nerve synapse

Clinical Syndromes

▼**Table 3–6.1B** *C. botulinum* Clinical Syndromes

Form	Acquisition	Signs	Diagnosis	Treatment	Prophylaxis
Infantile (floppy baby syndrome)	Ingestion of spores, toxi-infection	Constipation, limpness, dysphagia, weak feeding and crying, respiratory arrest, flaccid paralysis	Find toxin in serum or stool	Supportive	No honey for first year
Adult (food-borne)	Ingestion of toxin, in poorly canned alkaline vegetables, smoked fish	Descending weakness, dizziness, dryness of the mouth, blurred vision, nausea and vomiting, inability to swallow, difficulty in speech	Find toxin in leftover food or patient serum	Respiratory support, trivalent antitoxin	Proper canning, heating of food
Wound	Traumatic implantation of spores	No GI symptoms but otherwise as in adult form	Find toxin in serum	Delay closure, amoxicillin, antitoxin, respiratory support	Debridement

Courtesy of the Centers for Disease Control

Clostridium perfringens

Species Characteristics

- *Stormy fermentation* in milk media
- Nonmotile
- *Double zone of hemolysis*
- Positive *Nagler reaction* (egg yolk agar plate treated with anti-toxin antibodies shows lecithinase activity on untreated side)

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Reservoir/Transmission Soil/colon; traumatic implantation or foodborne

Pathogenic Features

- *Spores* germinate in tissues in anaerobic conditions
- *Alpha toxin (phospholipase C)* is a *lecithinase*; disrupts cell membranes, destroys RBCs, WBCs, platelets, endothelial cells, causes massive tissue destruction and hepatic toxicity
- Twelve other toxins
- Enterotoxin acts like *E. coli* LT to cause watery diarrhea

Clinical Syndromes

- **Gas Gangrene (Myonecrosis):**
  - Rapid, high mortality
  - Acute and extreme pain
  - Tissue fills with gas and edema
  - Fever, tachycardia, diaphoresis
- **Food Poisoning:** Noninflammatory diarrhea due to enterotoxin produced in gut, from reheated meat dishes

Diagnosis/Treatment

- **Gas Gangrene:**
  - Clinical diagnosis
  - Treatment: Debridement, delayed closure, clindamycin and penicillin, hyperbaric oxygen
- **Food Poisoning:** Clinical, self-limiting

Prophylaxis Debridement, penicillin

Biophoto Associates/Science Source

▲ **Figure 3-6.1G**
Nagler Reaction

Clostridium difficile

Species Characteristics

- Normal flora of the colon, overgrows when antibiotics kill competing flora
- Toxins A and B

Pathogenic Features

- **Toxin A:** Enterotoxin increases fluid loss, attracts granulocytes
- **Toxin B:** Cytotoxin

Clinical Syndromes *No. 1 nosocomial, antibiotic-associated diarrhea, pseudomembranous colitis*

Treatment

- Discontinue antibiotics if possible
- Severe disease: Metronidazole

Prophylaxis

- Caution with broad-spectrum antibiotics
- Isolation in nursing-home settings
- Autoclave bedpans

David M. Martin, M. D./Science Source

▲ **Figure 3-6.1H**
Endoscopy of Colon with Pseudomembranous Colitis

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6.2 Non-spore Forming

6.2.1 *Corynebacterium diphtheriae*

Genus/Species Characteristics

- Gram-positive rod
- Non-spore forming
- Aerobic

Reservoir/Transmission Throat, nasopharynx; bacterium or phage via respiratory droplets

Pathogenic Features

- Noninvasive organism; toxin becomes blood-borne
- Toxin *ADP-ribosylates eEF-2*
- *Toxin produced by lysogeny (β-corynephage)*
- Toxin binds to *heart, nerve, epithelial cells*

Clinical Syndrome

- **Diphtheria**
  - *Sore throat* with gray, dense *pseudomembrane* composed of dead cells, fibrin, bacterial pigment
  - Extension into trachea: *Obstruction*
  - Pseudomembrane *bleeds profusely* if dislodged
- **Myocarditis, Laryngeal Nerve Palsies, and Lower Limb Polyneuritides:** Due to circulation of toxin

Diagnostic Features

- Club-shaped rods in "Chinese character" forms
- Volutin granules stain metachromatically
- Gray-to-black colonies on tellurite agar
- Elek test is positive for toxigenic strains
- ELISA for toxin genes

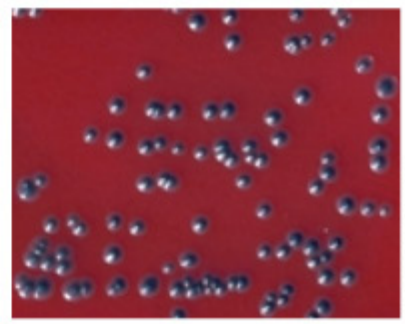
Treatment

- Erythromycin and antitoxin
- Endocarditis: Intravenous penicillin and aminoglycosides

Prophylaxis Formaldehyde-modified toxin in DTaP, boosters every 10 years

BSIP SA/Alamy

▲ **Figure 3-6.2A** Diphtheria Pseudomembrane



CDC/Dr. W.A. Clark

▲ **Figure 3-6.2B** Tellurite Agar

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6.2.2 *Listeria monocytogenes*

Genus/Species Characteristics

- Gram-positive rods
- Non-spore forming
- Cold growth
- Tumbling motility
- Facultative intracellular

Reservoir/Transmission

- Ubiquitous, animal GI and GU tracts
- Unpasteurized dairy, soft cheeses, deli foods
- Foodborne/transplacental/parturition

Pathogenic Features

- *Listeriolysin:* β-hemolysin facilitates escape from phagosome before lysosomal fusion
- Moves from cell to cell by actin filament formation

Clinical Syndromes

- **Adult/Foodborne**
  - Asymptomatic/diarrhea
  - Pregnant women: Septicemia with fever and chills can cause transplacental transmission
- **Neonatal**
  - Granulomatosis infantisepticum: Transplacental transmission; granulomatous septicemia with high mortality
  - Meningitis and septicemia (three to four weeks after birth): Acquired during parturition
- **Immunocompromised Patients:** No. 1 cause of septicemia and meningitis in renal transplant and cancer patients

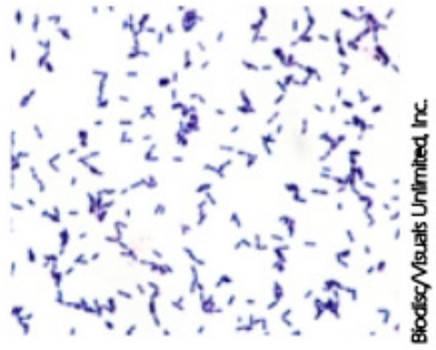
Diagnostic Features

- Blood or CSF culture
- Gram-positive, tumbling rods by cold enrichment

Treatment

- Ampicillin
- Add gentamicin for immunocompromised patients

Prophylaxis Pregnant and immunocompromised patients should avoid at-risk foods



▲ **Figure 3-6.2C**
Listeria monocytogenes

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6.3 Filamentous Bacteria

6.3.1 *Actinomyces israelii*

Genus/Species Characteristics

- Anaerobic
- Gram-positive branching, beaded rods
- Non-acid fast

Reservoir/Transmission

- Normal flora in anaerobic niches: Gingival crevices, portions of abdomen and female reproductive tract
- Spread endogenously

Pathogenic Features Invasive growth into areas with diminished oxygenation

Clinical Syndromes

- **Actinomycosis (non-mycotic mycetoma)**
- **Mycetomas:** Abscesses that drain through multiple sinus tracts and contain pus filled with yellow granular microcolonies
  - Cervicofacial (lumpy jaw): Associated with dental trauma or poor hygiene
  - Pelvic: IUDs
  - Abdominal: Bowel surgery or trauma

Diagnostic Features

- Culture microcolonies from pus
- Colonies resemble molar teeth

Treatment Ampicillin and penicillin G with surgical drainage

6.3.2 *Nocardia* spp. (*N. asteroides* and *N. brasiliensis*)

Genus/Species Characteristics

- Gram-positive rods
- Partially acid-fast
- Aerobic
- Filamentous

Reservoir/Transmission Soil and dust/airborne or traumatic implantation

Pathogenic Features

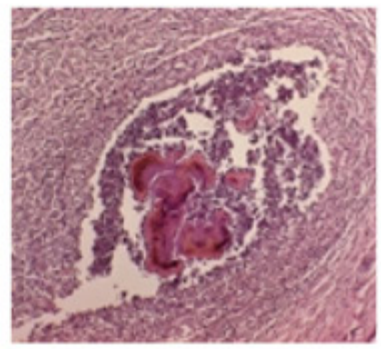
- No known toxins or virulence factors
- Immunosuppression and cancer predispose to lung infection

Clinical Syndromes *Nocardiosis*

- Cavitary bronchopulmonary disease: May spread hematogenously to the brain (mainly *N. asteroides*)
- Cutaneous/subcutaneous mycetomas (mainly *N. brasiliensis*)

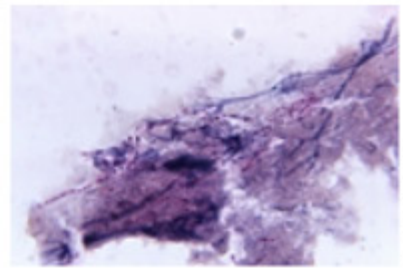
Diagnosis Culture sputum or mycetoma pus

Treatment Sulfonamides or trimethoprim-sulfamethoxazole



Dr. John D. Cunningham/Visuals Unlimited, Inc.

▲ **Figure 3-6.3A** Actinomycotic Mycetoma



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▲ **Figure 3-6.3B** Partially Acid-Fast: *Nocardia*

CDC/Dr. Libero Ajello

▲ **Figure 3-6.3C** Nocardial Mycetomas

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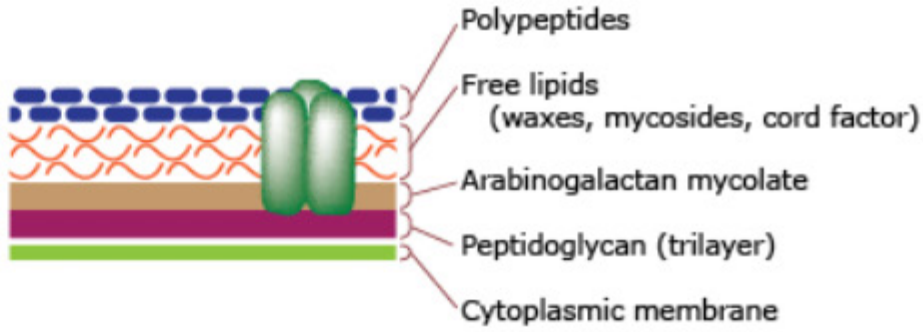
6.4 Acid-Fast, Gram-Positive Rods

6.4.1 *Mycobacterium*

Genus Characteristics

- **Acid-fast bacilli**
- **Obligate aerobe**
- **Sensitive to ultraviolet light**
- **Unique cell envelope:** Makes organism resistant to drying and chemicals



▲ **Figure 3-6.4A** Mycobacterial Cell Envelope

6.4.2 *M. tuberculosis*

Species Characteristics

- *Auramine-rhodamine staining*
- *Aerobic, slow-growing* (on Lowenstein-Jensen agar)
- *Produces niacin*
- *Heat-sensitive catalase:* Negative at 68°C; positive at body temperature

Reservoir/Transmission Human lungs/respiratory droplets

Pathogenic Features

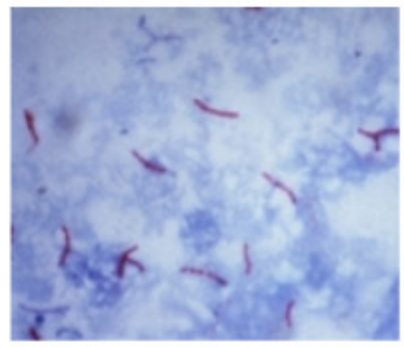
- **Facultative Intracellular** (granuloma former)
- **Cord Factor** (trehalose dimycolate)
  - Causes "cord-like" growth in vitro
  - *Inhibits leukocyte diapedesis*
  - *Disrupts mitochondrial respiration* and oxidative phosphorylation
  - *Strongest correlation to virulence overall*
- **Sulfatides**
  - Sulfolipids which *hydrolyze to produce* H_2SO_4
  - *Inhibit fusion of lysosome with phagosome*, allows intracellular survival
- **Mycobactin:** *Siderophore*, chelates iron
- **Tuberculin**

Clinical Syndromes Tuberculosis

- **Primary Pulmonary Disease**
  - Organisms replicate in alveolar macrophages until CMI begins *(Ghon focus)*
  - Macrophages transport bacilli to the mediastinal nodes *(Ghon complex)*
  - Many individuals heal without disease, but organisms that are walled off remain viable unless treated
- **Reactivational Disease**
  - Organisms begin to replicate again under conditions of diminished CMI
  - *Granulomas in the apices* due to high PO_2
- **Disseminated Disease (Miliary TB):** Granulomas may spread to any oxygen-rich location

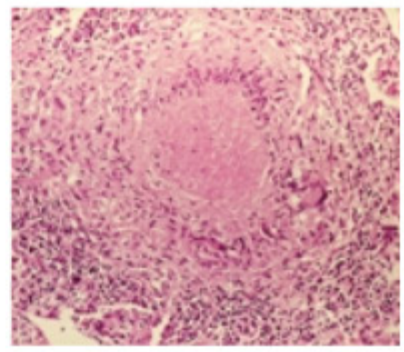
Living Art Enterprises, LLC/Science Source

▲ **Figure 3-6.4B** Tuberculous Meningitis



CDC/Dr. George P. Kubica

▲ **Figure 3-6.4C** Acid-Fast Bacilli: *Mycobacterium*



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▲ **Figure 3-6.4D** Tubercular Granuloma

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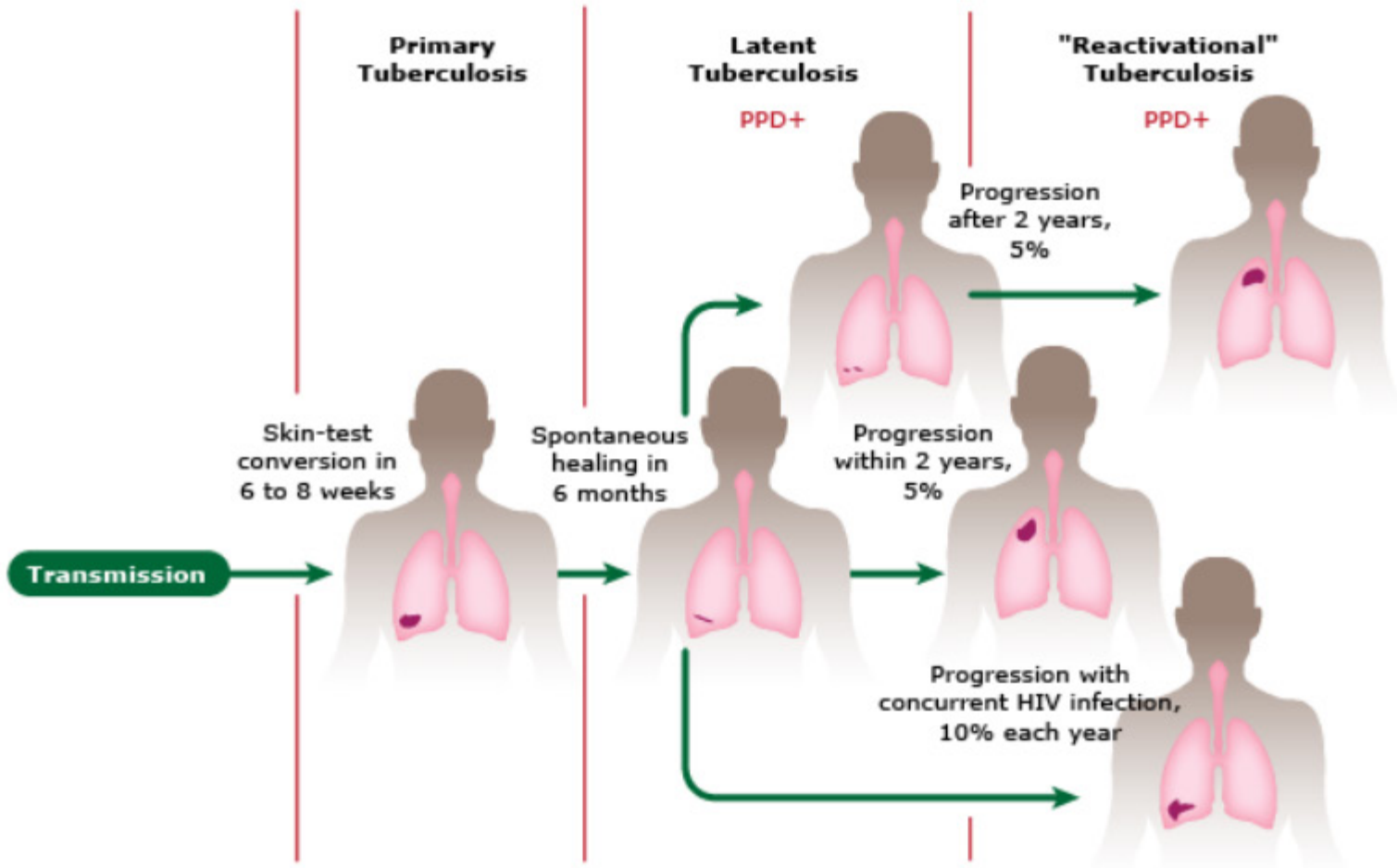

▲ **Figure 3-6.4E** Progression of Tuberculosis

Diagnostic Features

- Microscopy of sputum with *auramine-rhodamine dye* shows apple-green fluorescence
- *Confirm with acid-fast stain*
- *Niacin* production
- *Quantiferon* test: Measures interferon-γ production by Th cells exposed to tuberculin
- Skin test (Mantoux test, tuberculin test, type IV hypersensitivity)
- Positive skin test (indicates exposure but not necessarily active disease)
  - >5 mm: AIDS or immunosuppressed, recent contacts
  - >10 mm: Increased-risk individuals (health care workers, IV drug abusers, immigrants)
  - >15 mm: No known risk factors
- Chest x-ray: Treat if shows infection

Treatment

- Two months: Isoniazid, rifampin, and pyrazinamide
- Four months: Isoniazid and rifampin
- Ethambutol or streptomycin added in possible drug-resistant cases

Prophylaxis

- Isoniazid for nine months
- Bacille Calmette-Guérin (BCG) vaccine, live-attenuated, not used in U.S.; prevents dissemination but not pulmonary disease

SIU/Visuals Unlimited, Inc.

▲ **Figure 3-6.4F** Positive Tuberculin Test

BrazilPhotos.com/Alamy

▲ **Figure 3-6.4G** Primary TB: The Ghon Complex

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6.4.3 *M. leprae*

Species Characteristics

- Obligate intracellular (cannot be cultured)
- Prefers cooler body temperatures

Reservoir/Transmission Human nerves, mucosa, skin/prolonged contact

Clinical Syndromes

▼ **Table 3–6.4A** *M. leprae* Clinical Syndromes

Disease Characteristic	Tuberculoid	Borderline	Lepromatous
Cell-mediated immune system	Strong CMI Th1 response, IL-12 (macrophages)		Weak CMI Th2 response, IL-4
Lepromin skin test (type IV hypersensitivity)	Positive		Negative
Number of organisms in tissue	Low		High
Damage from	• Immune response (CMI killing infected cells) • Granuloma formation: Nerve enlargement/ damage • Loss of sensation: Burns and trauma		• Large number of intracellular organisms • Nerve damage from overgrowth of bacteria in cells • Loss of sensation: Burns and trauma
Number of lesions and other symptoms	Fewer lesions, macular, nerve enlargement, paresthesia		Numerous lesions becoming nodular—loss of eyebrows, destruction of nasal septum, paresthesia

Diagnostic Features

- Acid-fast bacilli in punch biopsy or nasal scrapings
- Lepromin skin test is positive only in the tuberculoid form

Treatment

- Dapsone and rifampin
- Clofazimine added for lepromatous cases

Science Source

▲ **Figure 3-6.4H** Lepromatous Leprosy

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6.4.4 Atypical Mycobacteria (Mycobacteria Other Than Tuberculosis; MOTTS)

Group Characteristics

- Noncontagious
- Sources in soil and water, cigarettes
- Runyon classification distinguishes them on the basis of production of yellow-orange pigments (*carotenoids*):
  - *Photochromogens:* Produce pigments after exposure to light
  - *Scotochromogens:* Produce pigments in the dark
  - *Non-chromogens:* Do not produce pigments

▼Table 3–6.4B Atypical Mycobacteria Characteristics

Species	Diagnosis	Source	Presentation	Patient	Treatment
M. avium intracellulare	Nonchromogen	Aerosol, ingestion	Pulmonary, gastrointestinal, disseminated	AIDS, cancer, chronic lung disease	Macrolide plus ethambutol, standard AIDS prophylaxis <50 CD4 cells
M. kansasii	Photochromogen				
M. marinum	Photochromogen	Fish tanks	Fish tank granuloma	Tropical fish enthusiasts	Isoniazid, rifampin, or ethambutol
M. scrofulaceum	Scotochromogen	Water sources	Solitary cervical lymphadenopathy	Children	Surgery

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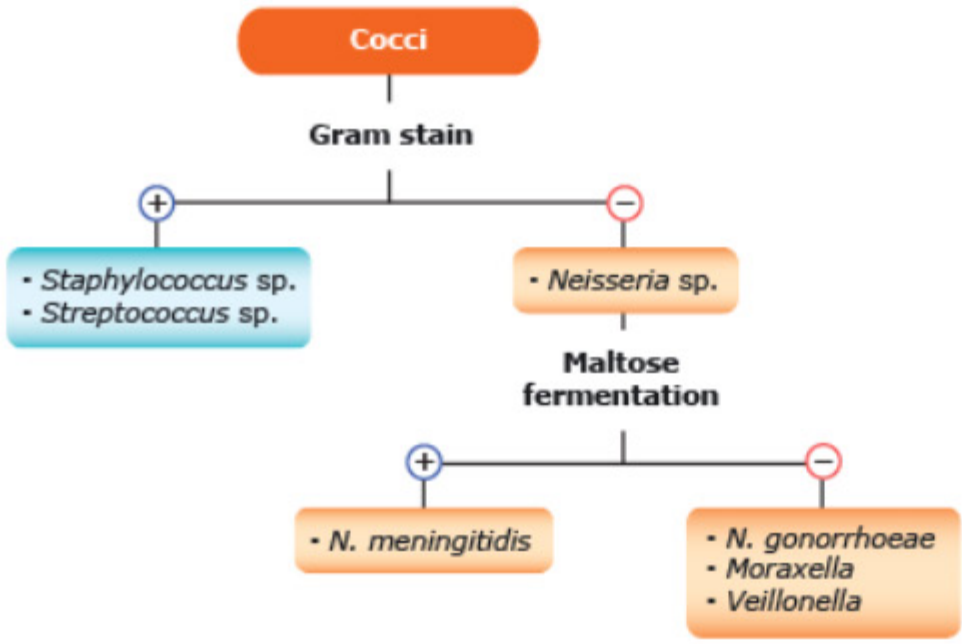
7 Gram-Negative Cocci

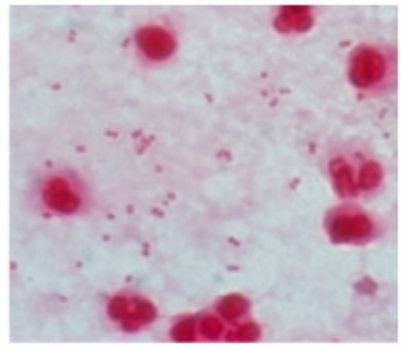


▲ **Figure 3-7.0** Laboratory Algorithm: Gram-Negative Cocci

7.1 *Neisseria*

7.1.1.Genus Characteristics

- Gram-negative
- Kidney-bean-shaped diplococci
- Oxidase positive



Michael Abbey/Science Source

▲ **Figure 3-7.1A** Gram-Negative Diplococci: *Neisseria*

7.1.2.Species Differentiation

▼ **Table 3–7.1** Gram-Negative Cocci: Species Differentiation

Species	Capsule	Vaccine	Source of Exposure	Maltose Utilization	Glucose Utilization	β-Lactamase Production
N. meningitidis	Yes	Yes	Respiratory	Yes	Yes	None
N. gonorrhoeae	No	No	Genital	No	Yes	Some

7.1.3 *N. meningitidis*

Species Characteristic

- Large capsule
- Oxidizes maltose and glucose

Reservoir/Transmission

- Human nasopharynx/respiratory droplets

Memory Aid

The **M**enin**G**ococcus oxidizes **M**altose and **G**lucose

The **G**onococcus only oxidizes **G**lucose

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Pathogenic Features

- **Lipooligosaccharide (LOS):** Same role as LPS but lacks repeating O-antigen subunits and has highly branched basal oligosaccharide; *blebs of membrane shed at all times*
- **IgA Protease:** Destroys local mucosal immunity
- **Pili and Outer-Membrane Proteins:** Mediate attachment
- **Capsule:** Polysaccharide, protects against phagocytosis, five serogroups
  - Four serogroups are immunogenic and included in the vaccine (Y, W-135, C, and A)
  - **Serogroup B capsule** = **sialic acid** (non-immunogenic): Causes 50% of infections in the U.S.

Clinical Syndromes

- **Meningococcemia and Meningitis:** Abrupt onset of fever, petechial rash, prostration
- **Waterhouse-Friderichsen Syndrome:** Hemorrhagic adrenalitis, ecchymoses, DIC, shock, coma, death
- Deficiency of membrane attack complex components (C5–C8) predisposes to repeated bacteremias

Diagnostic Features

- Gram stain of CSF: Gram-negative diplococci
- Culture on chocolate agar in 5% CO_2, oxidase-positive colonies
- PCR
- Latex particle agglutination to detect capsular serotype

Treatment

- Neonates and infants: Cefotaxime, ampicillin
- Older infants to adults: Cefotaxime or ceftriaxone, with or without vancomycin

Prophylaxis

- Vaccine: Capsule of strains Y, W-135, C, A
- Rifampin to contacts (reaches high concentration in saliva)

7.1.4 *N. gonorrhoeae*

Species Characteristics

- No capsule
- Oxidizes only glucose

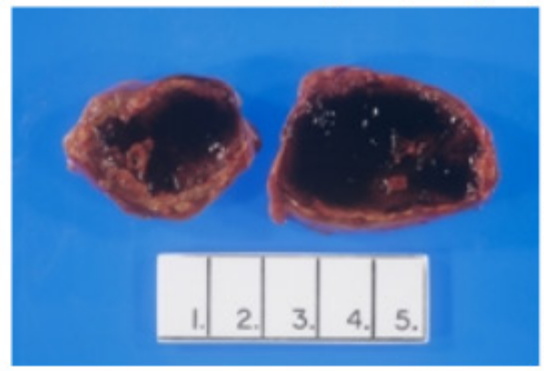
Reservoir/Transmission Human genital tract/sexual contact, parturition

Pathogenic Features

- **Pili**
  - Attachment to mucosa
  - Inhibit phagocytosis
  - Antigenic variation (more than 1 million variants)

Dr. Ken Greer/Visuals Unlimited, Inc.

▲ **Figure 3-7.1B** Meningococcal Disseminated Intravascular Coagulopathy



Dr. E. Walker/Science Source

▲ **Figure 3-7.1C** Waterhouse-Friderichsen Syndrome (Adrenals)

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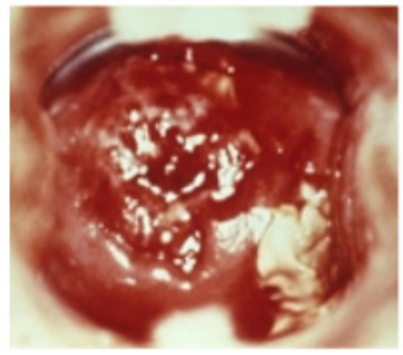
- **Outer-Membrane Proteins**
  - **Por Protein:** May prevent phagosome-lysosome fusion inside neutrophils
  - **Opa Proteins:** Adherence
- **IgA Protease:** Destroys local mucosal immunity
- **Lipooligosaccharide:** Endotoxic effects, causes ciliary loss and mucosal cell death in fallopian tubes
- *Invades mucosa, causes inflammation*

Clinical Syndromes

- **Gonorrhea**
  - **Male:** Urethritis, proctitis
  - **Female:** Endocervicitis, pelvic inflammatory disease, proctitis
- **Septic Arthritis:** More common in females, in knees, ankles, wrists
- **Ophthalmia Neonatorum:** Rapidly leads to blindness

Dr. P. Marazzi/Science Source

▲ **Figure 3-7.1D**
Gonococcal Urethritis



CDC/Dr. Paul Wiesner

▲ **Figure 3-7.1E**
Gonococcal Cervicitis

Diagnostic Features

- *Gram-negative diplococci inside PMNs* in the urethral exudate of males is diagnostic
- In females: *Culture on Thayer-Martin* or genetic probe is necessary to distinguish from normal flora
- Test for all other possible sexually transmitted infections

Treatment

- Ceftriaxone
- Plasmid-encoded β-lactamase provides high-level resistance to penicillin

Prophylaxis

- Safe sex
- Neonatal: Erythromycin ointment in eyes

Dr. M.A. Ansary/Science Source

▲ **Figure 3-7.1F**
Gonococcal Ophthalmia Neonatorum

7.2 *Moraxella catarrhalis*

Genus/Species Characteristics

- Gram-negative diplococcus
- Oxidase positive

Reservoir/Transmission Upper respiratory tract, normal flora

Clinical Syndromes Bronchitis, pneumonia, sinusitis, otitis media, conjunctivitis

Diagnostic Features Produces butyrate esterase (basis of rapid fluorometric test)

Treatment

- Amoxicillin plus clavulanate, trimethoprim-sulfamethoxazole, or second- or third-generation cephalosporin
- Most strains produce β-lactamase

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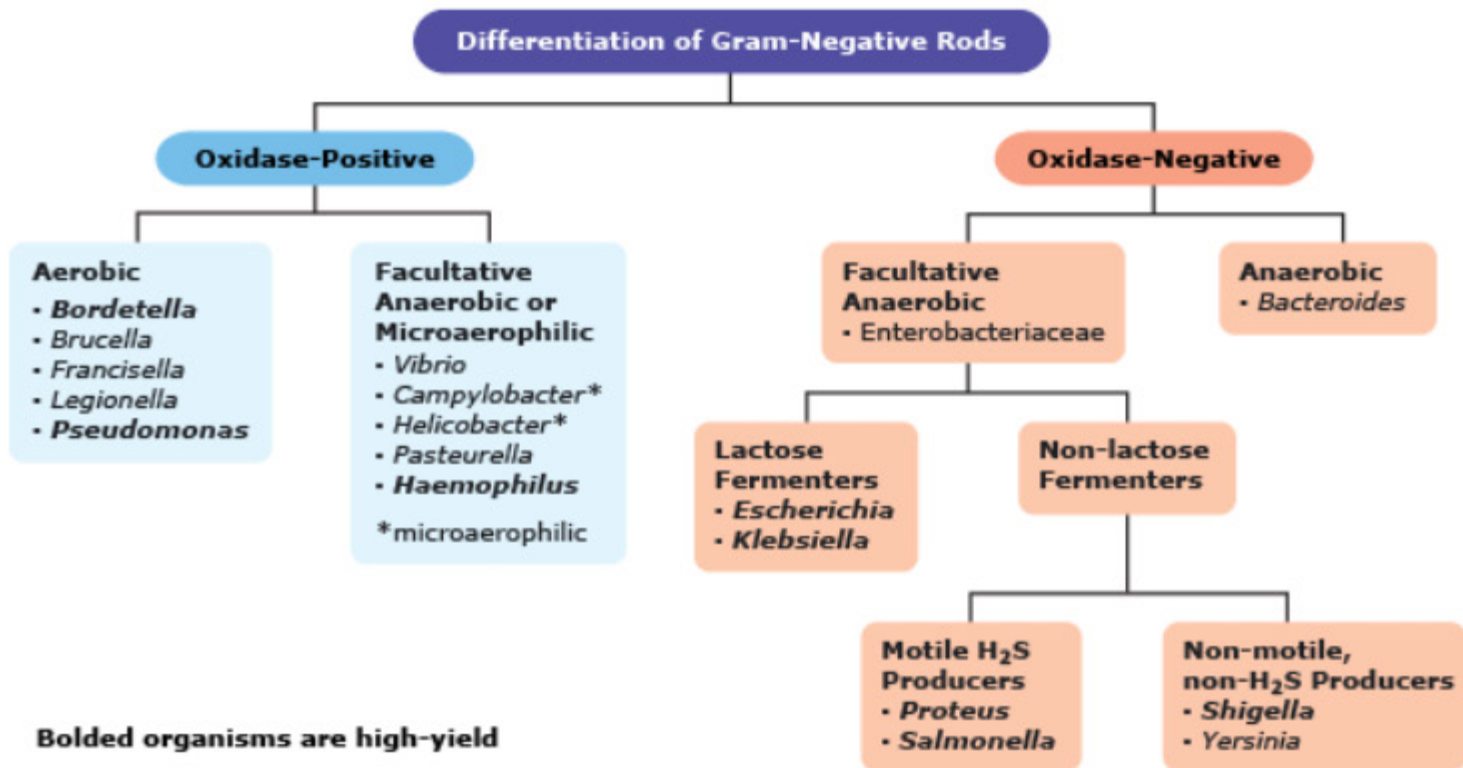
8 Gram-Negative Rods



▲ **Figure 3-8.0** Laboratory Algorithm: Gram-Negative Bacilli

8.1 Oxidase Positive

8.1.1 Aerobic

Bordetella pertussis

Species Characteristics

- Encapsulated
- Aerobic
- Gram-negative rod

Reservoir/Transmission

- Humans/respiratory droplets
- Adults vaccinated in childhood may transmit

Pathogenic Features

- **Mucosal Surface Pathogen:** Attachment by
  - Filamentous hemagglutinin
  - Pertussis toxin
- **Toxins** (chromosome-encoded)
  - **Pertussis Toxin:** (A/B toxin in outer membrane; ADP-ribosylates Gi keeping cyclase activity turned on and affecting multiple intracellular signaling pathways)
    - —Promotes lymphocytosis
    - —Sensitizes to histamine
    - —Enhances insulin secretion
    - —Promotes edema

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- **Tracheal Cytotoxin:** Inhibits DNA synthesis in ciliated cells
- **Dermonecrotic Toxin**
  - Vasoconstrictor
  - Necrosis of tracheal tissues
- **Adenylate Cyclase Toxin**
  - Inhibits chemotaxis and microbicidal function of PMNs and monocytes
  - Promotes edema

Clinical Syndrome Whooping Cough

The Stages of Whooping Cough (Pertussis) vs. Results of Bacterial Culture

	Incubation	Catarrhal	Paroxysmal	Convalescent
Duration	**7–10 days**	**1–2 weeks**	**2–4 weeks**	**1 month or longer**
Symptoms	None	Rhinorrhea, malaise, sneezing, anorexia, fever	Repetitive cough with whoops (air through narrowed glottis) vomiting, leukocytosis (up to 40,000/mm³)	Diminished paroxysmal cough, development of secondary complications (pneumonia, seizures, subconjunctival or cerebral hemorrhage, encephalopathy)
Bacterial Culture				

▲ **Figure 3-8.1A** Stages of Whooping Cough

Bubbles Photolibrary/Alamy

▲ **Figure 3-8.1B** Whooping Cough

Diagnostic Features

- Saline nasal wash cultured on Bordet-Gengou medium, identified by immunofluorescent staining
- Serologic tests, PCR available
- Unvaccinated child

Treatment Macrolides (erythromycin)

Prophylaxis Acellular pertussis component of DTaP contains filamentous hemagglutinin and pertussis toxin

Brucella spp.

Genus Characteristics

- Gram-negative, aerobic rods
- Zoonotic
- Facultative intracellular

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Reservoir/Transmission

- Domestic livestock/unpasteurized dairy, direct contact, travel to Mexico; California and Texas have highest number of cases
  - *B. melitensis* (goats)
  - *B. abortus* (cattle)
  - *B. suis* (pigs)

Pathogenic Features

- Endotoxin
- Granulomatous inflammation
- Facultative intracellular, causes septicemia

Clinical Syndrome Brucellosis

- Chronic illness with fever, night sweats, and weight loss
- Potential cycling of nocturnal fevers (undulant fever)

Diagnostic Clues

- Slow-growing in culture, serology

Treatment Doxycycline with an aminoglycoside

Prophylaxis Vaccinate livestock, pasteurize dairy foods; no human vaccine available

Francisella tularensis

Species Characteristics

- Small, gram-negative coccobacillus
- Requires cysteine and iron

Reservoir/Transmission

- Rabbits, deer, rodents/implantation, aerosol, ingestion
- Tick (*Dermacentor*) or deerfly (*Chrysops*)

Pathogenic Features

- Facultative intracellular
- Escapes phagosome to live in cytoplasm

Clinical Syndromes Tularemia

- Begins with fever, chills, malaise
- **Ulceroglandular:** Papule at inoculation site necroses and ulcerates
- **Oculoglandular:** Painful purulent conjunctivitis
- **Typhoidal:** Abdominal course mimicking typhoid fever
- **Pneumonic:** Resembles plague pneumonia

Diagnostic Clues

- A hunter in Arkansas, Missouri, or Oklahoma
- Serology, direct fluorescent antibody on biopsy material
- Culture is hazardous

Dr. Ken Greer/Visuals Unlimited, Inc.

▲ **Figure 3-8.1C** Ulceroglandular Tularemia

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Treatment Streptomycin or gentamicin

Prophylaxis

- Wear gloves when handling infected animals
- Avoid tick bite
- Live-attenuated vaccine for at-risk humans

Legionella pneumophila

Species Characteristics

- Weakly gram-negative rods
- Require cysteine and iron
- Facultative intracellular

Reservoir/Transmission

- Aerosols inhaled from water sources
- No human-to-human transmission

Pathogenic Features

- Facultative intracellular
- Inhibits phagosome-lysosome fusion
- Pore-forming toxin kills macrophages and facilitates spread
- Alveoli fill with exudate of fibrin, PMNs, macrophages, and RBCs

Clinical Syndromes

- **Legionnaires' Disease**
  - Atypical pneumonia
  - Confusion, delirium
  - Diarrhea
- **Pontiac Fever**
  - Self-limiting
  - Fever, myalgia, dry cough

Diagnostic Clues

- Patient is an elderly smoker with high alcohol intake or is immunosuppressed
- Dieterle silver stain or direct fluorescent antibody of biopsy
- Culture on buffered charcoal-yeast agar
- Urine antigen test

Treatment

- Fluoroquinolone, azithromycin, or erythromycin
- Add rifampin for immunocompromised patients

Prophylaxis

- Avoidance of contaminated water aerosols
- *Legionella* are resistant to chlorine and heat
- Silver and copper ionization systems to treat water sources

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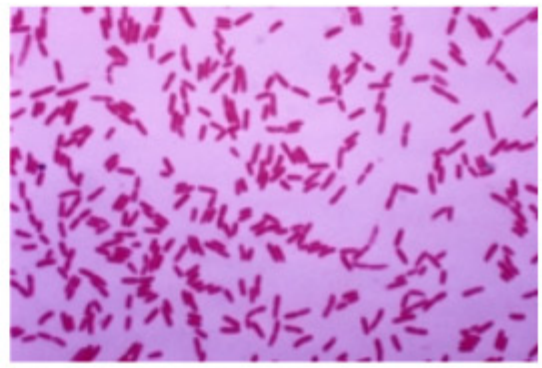
Pseudomonas aeruginosa

Species Characteristics

- Gram-negative, oxidase-positive bacillus
- Obligate aerobe (nonfermenter)
- Blue-green (pyocyanin) and fluorescent (fluorescein) pigments
- Fruity (grape-like) odor
- Alginate capsule (slime layer)



Dr. John D. Cunningham/Visuals Unlimited, Inc.

▲ **Figure 3-8.1D**
Encapsulated Gram-Negative Rods: *Pseudomonas*

Reservoir/Transmission Water/aerosols

Pathogenic Features

- Endotoxin
- Exotoxin A: ADP-ribosylates eEF-2, action like diphtheria toxin but primary target is the liver
- Capsule impedes phagocytosis
- Elastase: Hemorrhagic destruction of blood vessel walls

Clinical Syndromes

- Normal individuals
  - GI colonization: Transient diarrhea
  - Hot tub folliculitis
  - Eye ulcers: Trauma, prolonged contact lens wear
- Opportunistic infections
  - Cystic fibrosis patients: Pneumonia (No. 1 cause of death)
  - Burn patients: Cellulitis and septicemia, blue-green pus
  - Wounds exposed to water: Nail through tennis shoe
  - Neutropenic patients: Pneumonia and septicemia
  - Chronic granulomatous disease patients: Pneumonia and septicemia
  - Catheterized patients: Urinary tract infections

Diagnostic Clues

- Clinical: Patient population, blue-green pus, fruity odor
- Ecthyma gangrenosum: Classic lesion of pseudomonal septicemias; black necrotic center with raised hemorrhagic ring
- Gram stain, culture of nonfermenting colonies on EMB or MacConkey's agar

Robert Scheinbe/DermPicy/Science Source

▲ **Figure 3-8.1E**
Ecthyma Gangrenosum

Treatment

- Susceptibility testing: *P. aeruginosa* is the most consistently drug resistant of all of the pathogenic bacteria
- Anti-pseudomonal penicillin plus aminoglycoside

Prophylaxis

- Disinfection of any water-containing equipment
- Avoid having flowers or ice water baths in units with at-risk patients

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8.1.2 Microaerophilic

Campylobacter jejuni

Species Characteristics

- Gram-negative, curved rods
- Microaerophilic
- Grows at 42°C
- Oxidase positive
- Polar flagella ("seagull's wings")

Reservoir/Transmission Poultry/fecal-oral

Pathogenic Features

- Invades mucosa producing inflammatory diarrhea
- Low infectious dose (resistant to gastric acidity)
- Rarely produces septicemia

Clinical Syndromes

- **Gastroenteritis:** No. 1 bacterial cause in the U.S. (more than *Salmonella* and *Shigella* combined)
  - Blood and pus in stool, fever
  - Generally self-limiting in three to five days
- **Guillain-Barré syndrome (GBS):** Responsible for 30% of cases in the U.S. (serotype O:19 oligosaccharides cross-react with glycosphingolipids on neural tissue)
- Reactive arthritis

Diagnostic Features Culture on Campylobacter or Skirrow agar at 42°C in 5% O_2 and 10% CO_2

Treatment

- **Supportive:** Fluid and electrolytes
- **Severe:** Macrolides and fluoroquinolones

Helicobacter pylori

Species Characteristics

- Gram-negative, spirillar rods with flagella
- Oxidase positive
- Microaerophilic, best growth at 37°C
- Urease positive

Reservoir/Transmission Humans/fecal-oral, oral-oral

Pathogenic Features

- Urease neutralizes gastric acidity to allow survival
- Motility aids invasion
- Mucinase dissolves mucous covering of stomach lining
- Vacuolating cytotoxin kills cells and assists inflammation

A. Barry Dowsett/Science Source

▲ **Figure 3-8.1F**
Campylobacter jejuni

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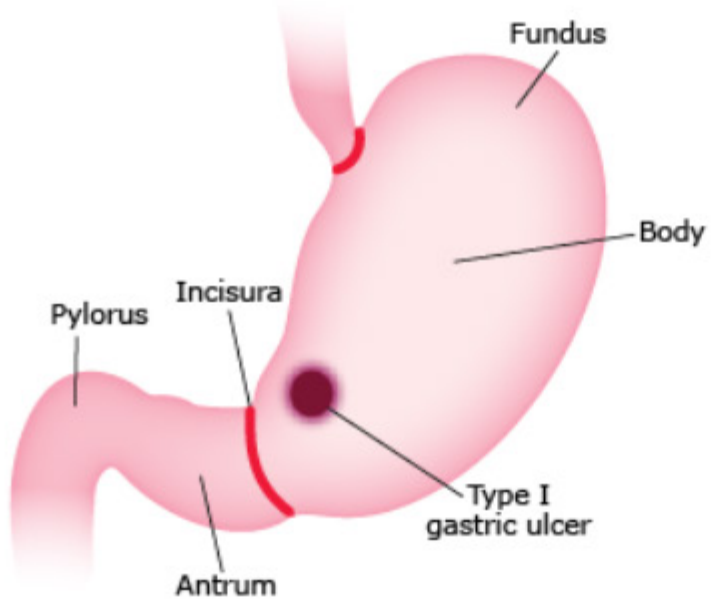
Clinical Syndromes

- Gastritis and ulcers
- Type I carcinogen: Gastric adenocarcinoma, MALT-oma, B cell lymphomas



▲ **Figure 3-8.1G** Sites of *Helicobacter* Lesions

Diagnostic Features

- Biopsy and culture
- Breath test (patient swallows radiolabeled C-urea and exhales radiolabeled CO_2)

Treatment Bismuth salts plus two antibiotics (metronidazole, tetracycline, clarithromycin, or amoxicillin)

8.1.3 Facultative Anaerobic

Vibrio spp.

Genus Characteristics

- Gram-negative, oxidase positive
- Polar flagella
- Comma-shaped, curved rods
- Prefer alkaline media

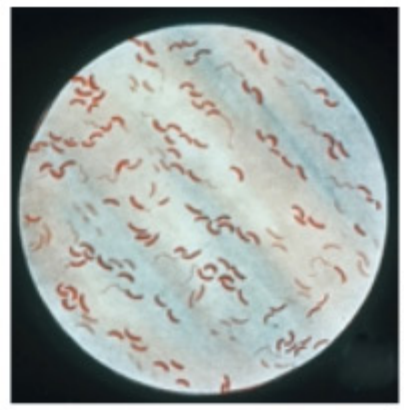
Vibrio cholerae

Species Characteristics

- Distinguished by O (envelope antigens); O1 and O139 cause cholera
- Produce cholera toxin

Reservoir/Transmission

- Human/fecal-oral, no carriers
- Shellfish may be contaminated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▲ **Figure 3-8.1H** Gram-Negative, Comma-Shaped Rods: *Vibrio*

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Pathogenic Features

- Sensitive to acidity, high infectious dose (10^7 organisms)
- Attachment via toxin coregulated pili, mucinase, motility
- **Cholera Toxin:** Choleragen
  - ADP ribosylates Gs alpha, activates adenylate cyclase, increases cAMP, and causes loss of Cl^- and water
  - Function similar to *E. coli* LT
  - Encoded in prophage (lysogeny)

Clinical Syndrome Cholera

- "Rice water" stools
- Hypovolemic shock
- Electrolyte imbalances

Diagnostic Features Culture of oxidase positive gram-negative curved rods on TCBS (thiosulfate citrate bile salts sucrose) agar

Treatment

- Fluids and electrolytes
- Doxycycline or ciprofloxacin may shorten course of the disease

Prophylaxis

- Proper sanitation, chlorination of water, cooking of shellfish
- Vaccines available for travelers (whole-cell, lipopolysaccharide, and toxin B subunit) but only live-attenuated vaccine strains produce local secretory IgA response

▼**Table 3–8.1** Other *Vibrio* Species

Species	Source	Syndrome	Symptoms	Treatment
V. parahaemolyticus	Marine, undercooked seafood	Gastroenteritis	Profuse, watery diarrhea	None required
V. vulnificus	Brackish water, oysters	Gastroenteritis following ingestion	Profuse, watery diarrhea	None required
		Cellulitis if introduced through abrasions	Rapidly spreading, ulcerative abscess	Tetracycline, third-generation cephalosporin

Haemophilus spp.

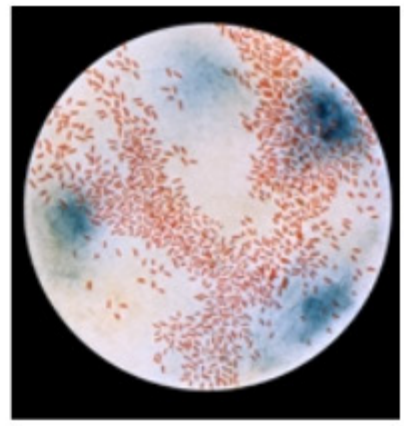
Genus Characteristics

- Gram-negative, coccobacilli
- Requires factors X (hemin) and V (NAD) for growth

Haemophilus influenzae

Species Characteristics

- Polyribitol phosphate capsule
- Type b capsule causes 90% of invasive disease



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▲**Figure 3-8.1l** Gram-Negative Pleomorphic Rods: *Haemophilus*

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Reservoir/Transmission Humans/respiratory droplets

Pathogenic Features
- Capsule prevents phagocytosis
- IgA protease

Clinical Syndromes
- Meningitis: 3-month- to 3-year-old, unvaccinated children
- Otitis media: Not typeable strains
- Bronchitis: Smokers with COPD
- Pneumonia: Smokers
- Epiglottitis: Unvaccinated children, major causal agent

Diagnostic Features
- Culture of blood or CSF on chocolate agar: Provides factors X and V
- Culture with *Staphylococcus aureus* on blood agar: Satellite phenomenon
- PCR
- Latex particle agglutination for capsular antigen detection

Treatment
- Cefotaxime or ceftriaxone
- Rifampin to reduce nasal carriage

Prophylaxis
- Hib vaccine, 95% effective, four doses
- Conjugated capsular polysaccharide-protein (T cell dependent) vaccine

Neil Borden/Living Art Enterprises, LLC/ Science Source

▲ **Figure 3-8.1J**
Thumb Sign

Haemophilus ducreyi

Reservoir/Transmission Humans/sexual transmission

Pathogenic Features
- Attachment: Pili and outer-membrane protein
- Toxin: Cytolethal distending toxin (kills T cells)

Clinical Syndrome Chancroid
- Soft, painful genital ulcer
- Common in Africa, Asia, India, and Latin America

Diagnostic Features
- Genus features for culture
- Clinical
- DNA probe

Treatment Azithromycin, ceftriaxone, ciprofloxacin, erythromycin

Prophylaxis Safe sex

Custom Medical Stock Photo

▲ **Figure 3-8.1K**
Chancroid

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Pasteurella

Genus Characteristics

- Gram-negative coccobacillus
- Oxidase positive

Reservoir/Transmission Cat and dog mouths; bites, scratches

Pathogenic Features

- Endotoxin
- Capsule

Clinical Syndromes Cellulitis, wound infections

Diagnostic Features Rarely cultured, grows on blood agar

Treatment Amoxicillin, clavulanate

Other Bacteria Associated With Bites

Because the clinical therapy of bite wounds is always the same, there is little purpose in culture or identification of microorganisms within the wound. Bite wounds, regardless of source, are cleaned carefully and the patient is given a course of broad-spectrum antibiotics. If, however, the USMLE asks what organism is most likely to be transmitted by the bite of a particular animal, here are the facts:

- Cat bite (although found in many animal mouths): *Pasteurella multocida*
- Cat scratches: *Bartonella henselae*
- Dog bite: *Capnocytophaga canimorsus*
- Human bite (or fist fight): *Eikenella corrodens*
- Rat bite: *Streptobacillus moniliformis*

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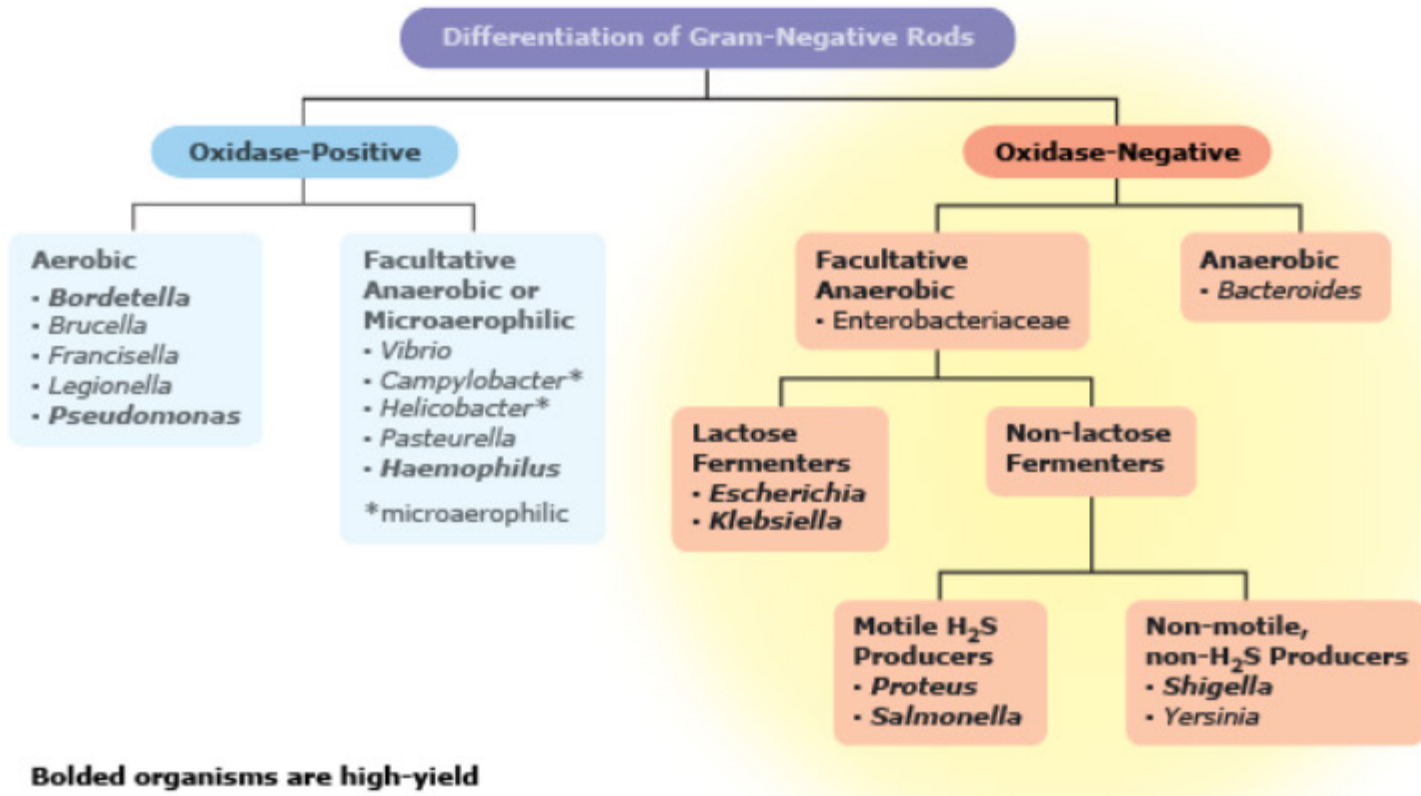
8.2 Oxidase Negative



▲ **Figure 3-8.2A** Laboratory Algorithm: Gram-Negative Rods: Oxidase Negative

8.2.1 Facultative Anaerobic

Enterobacteriaceae

Family Characteristics

- Gram-negative bacilli
- Facultative anaerobes
- Ferment glucose
- Catalase positive
- Oxidase negative (do not use cytochrome c oxidase as their terminal electron acceptor)
- Use nitrate as their terminal electron acceptor, reducing it to nitrite
- All have endotoxin
- Some produce exotoxins
- Distinguished by antigens:
  - O: Envelope
  - H: Flagellar
  - K: Capsule
  - Vi (virulence): Capsule of *Salmonella*

Lactose Fermenters Produce colored colonies on eosin methylene blue (EMB) or MacConkey agar

- *Citrobacter*
- *Enterobacter*
- *Escherichia*
- *Klebsiella*

Carolina Biological Supply Co./Visuals Unlimited, Inc.

▲ **Figure 3-8.2B** Metallic Green Sheen on Eosin Methylene Blue Agar

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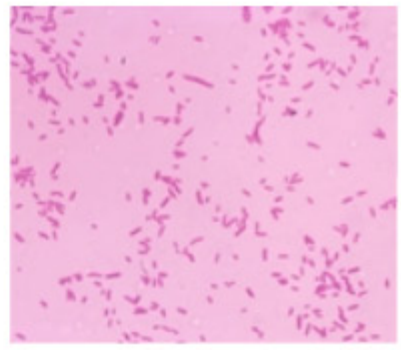
Escherichia coli

Genus Characteristics Gram-negative, oxidase negative, lactose-fermenting rod

Reservoir/Transmission

- Human colonic normal flora
- Endogenous
- Mother to child during delivery
- Fecal-oral contamination of food
- Enterohemorrhagic strains: Cattle feces

Pathogenic Features



Biophoto Associates/Science Source

▲ **Figure 3-8.2C** *Escherichia coli* Gram Stain

▼ **Table 3–8.2** Pathogenic Features of *Escherichia*

Clinical Presentation	Pathogenesis	Diagnostic Clues	Treatment
Urinary tract infection (No. 1 cause)	• Transmission from normal flora • Motility aids movement against urine flow • Adherence via P-pili, X-adhesins • Many are β-hemolytic	Gram-negative bacilli, 10^5 CFU/mL, nitrite positive urine	Fluoroquinolones or sulfonamides
Neonatal meningitis or septicemia (No. 2 cause)	• Maternal fecal flora contaminate during delivery • Endotoxin • Most have K1 capsule	Gram-negative bacilli in CSF or blood culture	Ceftriaxone
Septicemia	• Contamination through indwelling vascular catheters or damage from cytotoxic drugs allows escape from intestine • Endotoxin	Blood culture, gram-negative, oxidase-negative bacilli	Fluoroquinolones, third-generation cephalosporins
Gastroenteritis strains (all fecal-oral in transmission)			
EAEC (enteroaggregative *E. coli*)	Pili, biofilm production	• Watery diarrhea • Infants and children in developing world	Stacked-brick biofilm on mammalian cells
EHEC (enterohemorrhagic *E. coli*; 0157:H7 most common)	Bovine source, verotoxin (Shiga-like) shuts down protein synthesis by interfering with 60S ribosomal subunit	• No fever, no pus, but bloody diarrhea • Progression to HUS and hemorrhagic colitis, no sorbitol fermentation • Most severe in children under 5	Antibiotics contraindicated: May increase risk of HUS
EIEC (enteroinvasive *E. coli*)	Invades colon	• Inflammatory diarrhea (blood, pus, fever) • Children under 5 in the developing world	Trimethoprim sulfamethoxazole or fluoroquinolones
EPEC (enteropathogenic *E. coli*)	Bundle-forming pili promote attachment/effacing lesions	• Infants • Developing world	β-lactams, macrolides
ETEC (enterotoxigenic *E. coli*)	• Colonizing factor adhesins mediate attachment to mucosa • Capsule, LT stimulates adenylate cyclase by ADP ribosylation of Gs • ST stimulates guanylate cyclase	• Traveler's diarrhea • Noninflammatory • Immunoassay for enterotoxin	Rehydration, trimethoprim-sulfamethoxazole only in severe cases

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Klebsiella pneumoniae

Species Characteristics

- Enterobacteriaceae, lactose fermenter
- Encapsulated, nonmotile

Reservoir/Transmission Human colon and upper respiratory tract/endogenous

Pathogenic Features

- Large capsule interferes with complement activation and impedes phagocytosis
- Pili mediate attachment
- Endotoxin

Clinical Syndromes

- **Pneumonia:**
  - Typical pneumonia with many abscesses
  - Thick, gelatinous sputum (currant jelly)
  - Patient with chronic lung disease or alcoholism
  - High fatality and drug resistance
- **Urinary Tract Infections:** Fecal contamination of catheters (nosocomial)
- **Septicemia:** Immunocompromised patients from invasion of IV lines or bowel defects

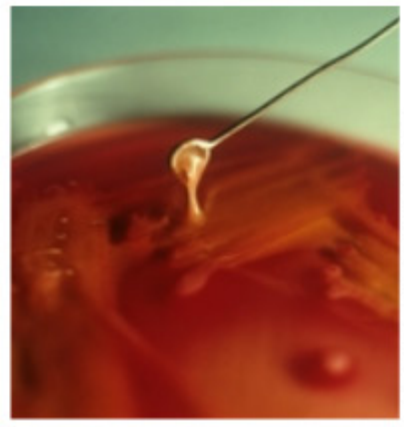
Diagnostic Features

- Culture of sputum or urine
- Lactose fermenting, gram-negative, oxidase negative bacillus

Treatment

- Fluoroquinolones, third-generation cephalosporin with or without aminoglycoside
- Among the most drug resistant of the enterobacteriaceae

Prophylaxis Limit use of catheters



Laurie Jensen/Visuals Unlimited, Inc.

▲ **Figure 3-8.2D**
Mucoid Growth of *Klebsiella pneumoniae*

Non-lactose Fermenters

Motile, H_2S Producers

Proteus mirabilis, P. vulgaris

Genus Characteristics

- Enterobacteriaceae, non-lactose fermenting
- Peritrichous flagella: Swarming motility
- Urease positive

Reservoir/Transmission Human colon and environment/endogenous or from water, soil

Pathogenic Features

- Motility aids movement against flow of urine
- Urease raises urinary pH and causes struvite or staghorn stones
- Endotoxin important in septicemias

Southern Illinois University/Science Source

▲ **Figure 3-8.2E**
Staghorn Renal Calculus

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Clinical Syndromes

- Urinary tract infections
- Kidney stones
- Septicemia

Diagnostic Features

- Culture of blood or urine
- Lactose non-fermenting enterobacteriaceae
- Urease positive (ammoniac odor to urine and raised pH)

Treatment Fluoroquinolones, third-generation cephalosporin, trimethoprim-sulfamethoxazole

Salmonella enterica serovars

Genus Characteristics

- Enterobacteriaceae
- Non-lactose fermenters
- Produce H_2S gas
- Motile
- Over 2,000 serovars of one species are distinguished by O, H, and Vi antigens

S. enterica serovar Typhi

Serovar Characteristics

- Vi polysaccharide capsule
- Infects humans only and produces carrier state

Reservoir/Transmission Human colon; fecal-oral from carrier

Pathogenic Features

- High infectious dose required (10^5)
- Pili attach to D-mannose receptors
- Vi capsule protects from phagocytosis, impedes phagocyte respiratory burst and may inhibit toll-like receptor responses
- Facultative intracellular

Clinical Syndrome Typhoid fever, enteric fever

- Infection begins in ileocecum with constipation common
- Organisms taken up by M cell ruffles and allowed to transcytose to the basolateral membrane
- Organisms taken up by macrophages are carried throughout lymphatic circulation to mesenteric nodes, spleen, liver, and bone marrow
- At one week, 80% of patients have positive blood cultures and 25% have rose spots on trunk and abdomen
- Organisms are carried to the liver and into the biliary system; they reenter the intestine and by the third week, 85% of stool cultures are positive

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Diagnostic Features

- Traveler to endemic area
- Extended fever and abdominal pain
- Rose spots on abdomen
- Culture of blood or feces, non-lactose fermenting, H_2S producing gram-negative bacilli
- Serologic determination of O, H, and Vi antigens (Widal test)

Treatment Ceftriaxone, cefixime, ciprofloxacin

Prophylaxis

- Provision for clean water supplies
- Treatment of carriers
- Old vaccines: Whole killed bacteria, live-attenuated and Vi antigen
- New vaccine: Vi antigen conjugated to a bacterial protein

Nontyphoidal Salmonellae

Serovar Characteristics As with *S. enterica* serovar Typhi, except capsules are not important

Reservoir/Transmission Poultry products, reptile pets

Pathogenic Features

- High infectious dose required (10^5)
- Pili attach to D-mannose receptors
- Organisms invade to lamina propria, induce inflammation, kill macrophages, induce prostaglandin synthesis
- Prostaglandins increase cAMP, cause fluid loss

Clinical Syndromes

- Gastroenteritis: 6- to 48-hour incubation, nausea, vomiting, fever, only occasionally bloody
- Septicemia: Uncommon unless patient is elderly or very young
- Osteomyelitis: No. 1 cause in sickle cell patients

Diagnostic Features

- Stool culture on Hektoen agar, H_2S production
- Serotype by serologic analysis of O, H antigens (Widal test)

Treatment

- Fluid and electrolyte replacement
- Antimicrobics increase potential for carrier state

Prophylaxis Proper preparation of food; hand washing

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Nonmotile, Non-H_2S Producers

Shigella spp.

Genus Characteristics

- Enterobacteriaceae
- Non-lactose fermenter, nonmotile

Reservoir/Transmission

- Human colon/fecal-oral
- No carrier state

Pathogenic Features

- Extremely acid resistant: 1 to 10 organisms required
- Organisms invade M cells, replicate, create actin jet trails to move laterally along epithelium
- Shallow ulcers, rarely invasion to blood vessels (*S. sonnei*), deeper invasion with other species
- Shiga toxin (produced by *S. dysenteriae*, type 1, not by *S. sonnei*; most common in the U.S.)
  - Neurotoxic, cytotoxic, enterotoxic
  - Inhibits protein synthesis by clipping 60S ribosomal subunit

Clinical Syndromes

- Shigellosis (enterocolitis to dysentery)
- Fever, cramps, tenesmus
- Diarrhea is first watery, then bloody

Diagnostic Features

- Stool culture on Hektoen agar
- Slide agglutination tests to determine O antigen

Treatment Disease is self-limiting, but trimethoprim-sulfamethoxazole, fluoroquinolones, or cefriaxone can be used to shorten duration of illness

Prophylaxis Standard sanitation

Yersinia spp.

Genus Characteristics

- Enterobacteriaceae
- Non-lactose fermenter, nonmotile, non-H_2S producer
- Bipolar staining
- Zoonotic

Yersinia pseudotuberculosis and *Y. enterocolitica* (enteropathogenic *Yersinia*)

Reservoir/Transmission

- Zoonotic/unpasteurized milk, pork
- Northern climates (Scandinavia, other parts of northern Europe)

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Pathogenic Features

- Multiplies in the cold
- Invades M cells
- Invasins
- Major effector proteins: Yops

Clinical Syndromes

- Acute mesenteric lymphadenitis (pseudoappendicitis) in children
- Enterocolitis
- Polyarthritis associated with diarrhea

Diagnostic Features Stool culture at 25°C, cold enrichment

Treatment

- Usually self-limiting
- Immunocompromised patients: Fluoroquinolones or third-generation cephalosporins

Prophylaxis

- Pasteurization of dairy products
- Proper cooking of pork

Yersinia pestis

Reservoir/Transmission

- Zoonotic, rodents/flea bite
- Pneumonic form: Human to human
- U.S. desert southwest

Pathogenic Features

- Coagulase clogs mouthparts of flea and increases transmission
- Facultative intracellular
- Endotoxin and Yops
- Envelope antigen (F1) antiphagocytic

Clinical Syndromes

- Bubonic plague
  - Flea bite or contact with infected animal
  - Rapid increase in fever
  - Regional buboes (hemorrhagic lymph nodes)
  - Conjunctivitis
  - Septicemia and death
- Pneumonic plague
  - Spread to lung from bubonic form or inhalation from infected human
  - Much more rapid progression to death by septicemia

CDC/Science Source

▲ **Figure 3-8.2F**
Disseminated Intravascular Coagulation From Plague

CDC/Science Source

▲ **Figure 3-8.2G**
Bubonic Plague Buboes

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Diagnostic Features

- Specimens and cultures are hazardous
- Serodiagnosis or direct immunofluorescence

Treatment

- Aminoglycosides
- 72-hour quarantine after drug initiation

Prophylaxis

- Killed vaccine (military)
- Animal control

8.2.2 Anaerobic

Bacteroides fragilis

Genus Characteristics

- Gram-negative bacillus
- Obligate anaerobe (aerotolerant, produce superoxide dismutase)
- Endotoxin is missing part of lipid A

Reservoir/Transmission Human colon/endogenous

Pathogenic Features

- Oxygen tolerance allows it to live in mixed cultures
- Pili: Adherence
- Capsule causes abscess formation

Clinical Syndromes Peritonitis, septicemia

Diagnostic Features

- Patient with abdominal trauma, bowel defects, cytotoxic drug use
- Generally treated presumptively

Treatment Metronidazole, cefoxitin, clindamycin

Prophylaxis Antibiotics administered prophylactically before gastrointestinal surgery

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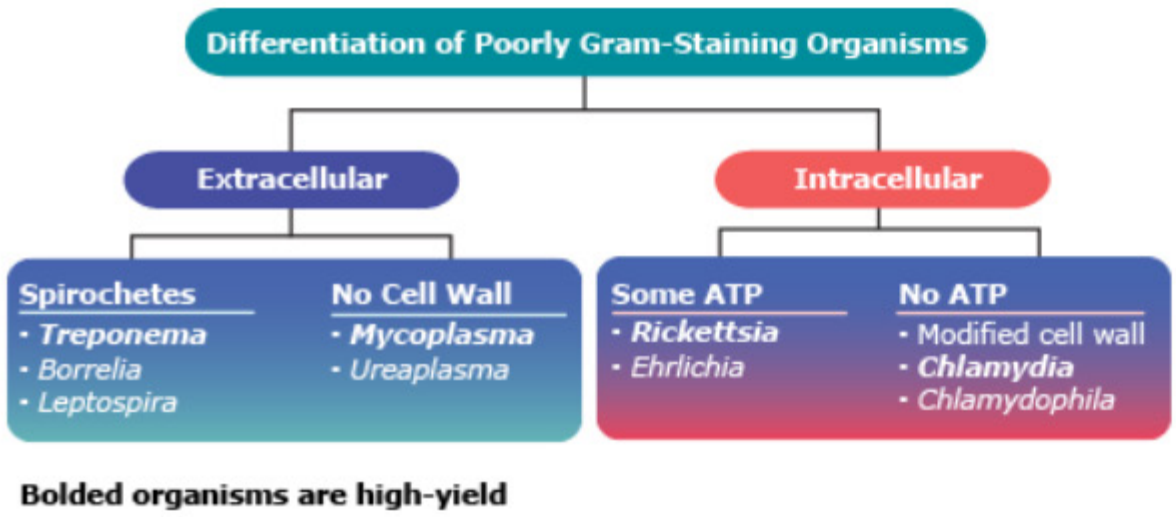
9 Spirochetes



▲ **Figure 3-9.0** Laboratory Algorithm: Atypical Bacteria

9.1 Order Characteristics

- Spiral morphology
- Motile via endoflagellum (axial filament)
- Gram-negative morphology
- Difficult to culture

9.2 *Treponema pallidum*

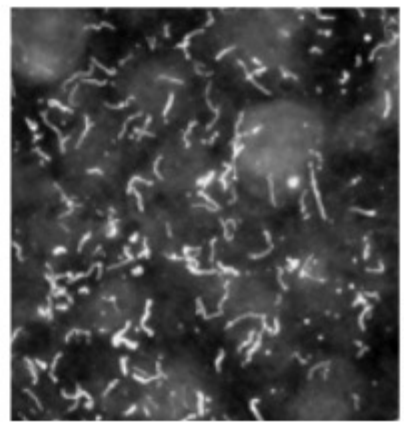
Species Characteristics

- Corkscrew spirals
- Visible by dark-field microscopy

Reservoir/Transmission Human genital tract/sexual, transplacental, transfusion

Pathogenic Features

- Endotoxin
- Primary lesion: Endarteritis with swelling and proliferation of endothelial cells
- Granulomatous cuffs of lymphocytes, monocytes, and plasma cells surround vessels
- Jarisch-Herxheimer reaction: Endotoxin shock response, which starts in first 24 hours of drug treatment (fever, fall in blood pressure, leukopenia, rigors)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▲ **Figure 3-9.2** Darkfield Microscopy of *Treponema pallidum*

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Clinical Syndromes

▼Table 3–9.2 Syphilis: Clinical Syndromes

Stage	Onset	Signs and Symptoms	Diagnostic Technique	Therapy
Primary	10 days to 3 months after exposure	Painless, indurated chancre on genitalia, heals spontaneously in 3 to 6 weeks	Biopsy or scraping observed with dark-field microscopy; serology usually negative	Benzathine penicillin
Secondary	1 to 3 months later	Generalized bronzing maculopapular rash, involves palms and soles, alopecia, condylomata lata	Serology: Nonspecific test confirmed by specific test	Benzathine penicillin
Latent		None	Nonspecific and specific serologic tests are positive	Benzathine penicillin
Tertiary	5 to 20 years after initial infection (one third of patients)	Syphilitic granulomas (gummas) in vasculature, tabes dorsalis	Specific serology only, nonspecific tests may revert to negative	Penicillin G
Congenital syphilis		Rhinitis, rash of secondary stage disease, bone deformations	Treponemal IgM tests	Penicillin G

1. SPL/Science Source; 2. Martin M. Rotker/Science Source

Diagnostic Tests

- **Non-treponemal (nonspecific) serologic tests**
  - Detect antibodies (reagin) against mammalian cardiolipin
  - VDRL: Venereal disease research laboratory
  - RPR: Rapid plasma reagin
  - Inexpensive and readily available, but titers decline with time
- **Treponemal (specific) serologic tests**
  - FTA-ABS: Fluorescent treponemal antibody-absorption
  - MHA-TP: Microhemagglutination using treponemal antigens on erythrocytes
  - More expensive, less readily available

Prophylaxis

- Safe sex
- Contact tracing
- Benzathine penicillin to contacts

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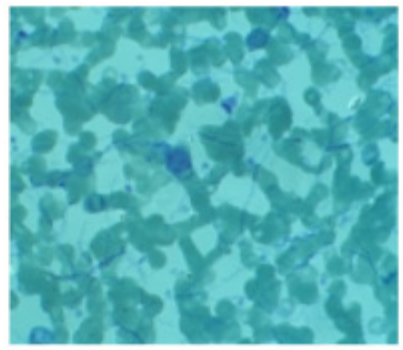
9.3 *Borrelia burgdorferi*


Sinclair Stammers/Science Source

▲ **Figure 3-9.3A** *Borrelia burgdorferi*

Scott Camazine/Science Source

▲ **Figure 3-9.3B** *Ixodes dammini* (3 instars)

Species Characteristics

- Loose spirals
- Microaerophilic

Reservoir/Transmission Ticks (*Ixodes*), mice, and deer/tick bite

Pathogenic Features

- Lacks classic endotoxin
- Outer surface proteins (Osps) inhibit complement fixation
- Inflammation stimulated by cell wall peptidoglycan
- Arthritis has aspects of autoimmunity

Clinical Syndromes

▼ **Table 3–9.3** Lyme Disease (Borreliosis): Clinical Syndromes

Stage	Onset	Pathogenesis	Signs
Early localized	Within a month	Organism inoculated with tick bite	Target-shaped (bull's-eye) rash (erythema migrans), fever, fatigue, myalgia, headache, joint pains, mild neck stiffness Science Source
Dissemination	Days, weeks, months	Organism disseminates	Fluctuating meningitis, cranial nerve palsies, peripheral neuropathy; cardiac conduction abnormalities (AV block) or myocarditis
Chronic persistent	Weeks to years	Autoimmune? Type III hypersensitivity?	Fluctuating arthritis, large joints, chronic neurologic dysfunctions

Diagnostic Features

- Enzyme immunoassay followed by Western blot
- Early infections often seronegative; many false positives
- Clinical, exposure

Treatment Doxycycline and amoxicillin

Prophylaxis Avoid tick bite

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9.4 *Leptospira interrogans*

Species Characteristics Close spirals with hooked ends

Reservoir/Transmission Rodents, cattle, dogs/exposure to water contaminated with urine; enters through breaks in skin or mucosa

Pathogenic Features

- Active motility of hooked ends may allow organism to burrow into tissues
- Spreads via bloodstream to CNS, kidney

Clinical Syndromes

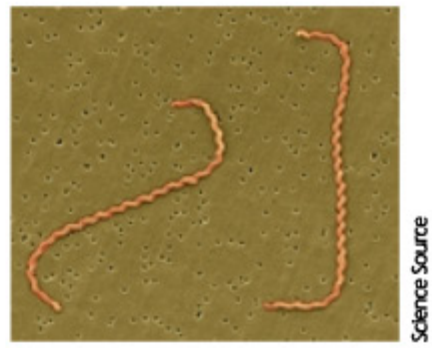
- Leptospirosis: Flu-like prodrome with fever, nausea, vomiting, headache, abdominal pain, myalgia
- Weil disease: Vasculitis, jaundice, renal damage, hemorrhagic rash

Diagnostic Features

- Occupational or recreational exposure to water
- Highest incidence is in Hawaii
- Serology: Agglutination

Treatment Penicillin, doxycycline, or ceftriaxone

Prevention Vaccines in cattle and domestic animals


Science Source

▲ **Figure 3-9.4**
Leptospira interrogans

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10 Unusual Bacteria

▼**Table 3–10.0** Unusual Bacteria

Characteristic	Chlamydiaceae	Rickettsiaceae	Mycoplasmataceae
Free-living	No, obligate intracellular	No, obligate intracellular	Yes
ATP production	None	Limited	Normal
Cell wall	Peptidoglycan lacks muramic acid	Normal peptidoglycan	No cell wall, sterols in cell membrane

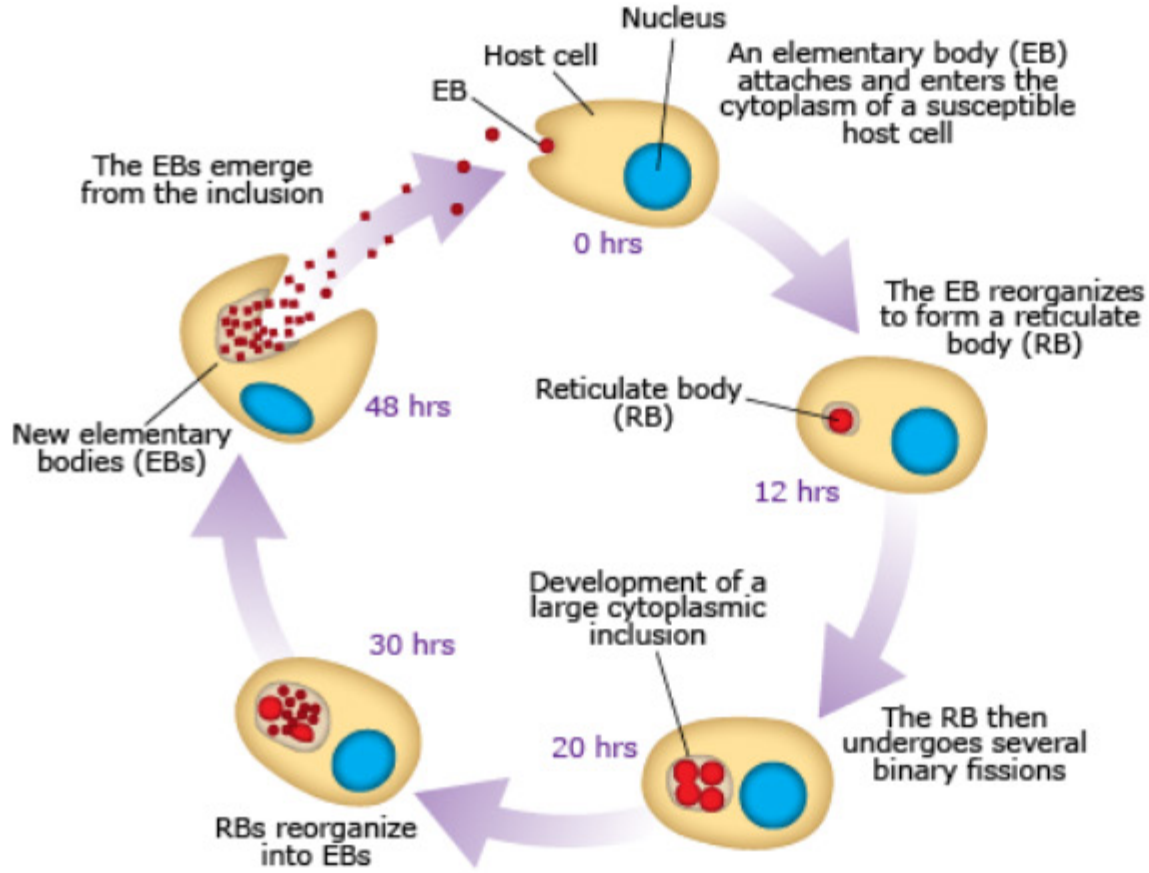
10.1 Family Chlamydiaceae

10.1.1 *Chlamydia trachomatis*

Genus Characteristics

- Poorly Gram staining
- Obligate intracellular in epithelial cells

Reservoir/Transmission Human conjunctiva and genital tract/ hand-to-eye or sexual transmission



▲**Figure 3-10.1A** Chlamydia Life Cycle

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Pathogenic Features

- Organism has tropism for epithelial cells of endocervix and upper genital tract of women and urethra, rectum, and conjunctiva of both genders
- IL-8 is released by infected cells and causes early tissue infiltrates with PMNs, replaced later with lymphocytes, macrophages, plasma cells
- Obligate intracellular
- Granulomatous inflammation results in fibrosis and scarring

Clinical Syndromes

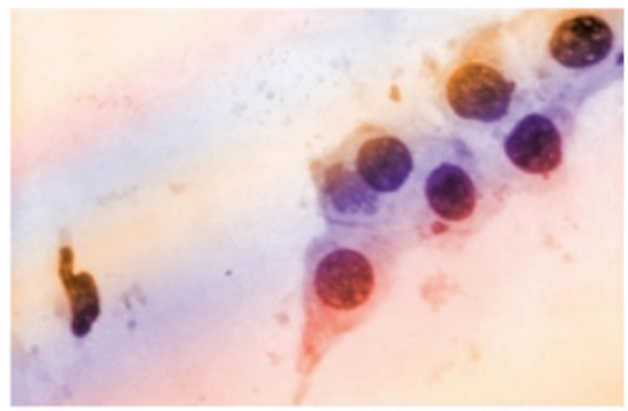
- Trachoma
  - Serotypes A, B, Ba, and C
  - No. 1 cause of infectious preventable blindness worldwide
  - Granulomatous inflammation leads to entropion and scarring
- Sexually transmitted infection serotypes D-K (No. 1 bacterial STI in the U.S.)
  - Nongonococcal urethritis, cervicitis, PID, infertility
  - Inclusion conjunctivitis in neonates
  - Atypical pneumonia in neonates
- Lymphogranuloma venereum
  - Serotypes L1,2,3
  - Common in Africa, Asia, and South America
  - Transient genital lesion followed by multilocular suppurative involvement of the inguinal lymph nodes

Diagnostic Features

- Scraping of affected area: Female cervix, male urethra, ocular conjunctiva
- Intracytoplasmic inclusions in epithelia
- Tissue culture

Treatment Tetracyclines, macrolides

Prevention Erythromycin ointment in neonatal eyes



CDC/PHANIE/Science Source

▲ **Figure 3-10.1B** Chlamydial Reticulate Bodies

10.1.2 *Chlamydophila psittaci*

Reservoir/Transmission Birds, parrots, turkeys; inhalation of excreta

Pathogenic Features Obligate intracellular, atypical pneumonia

Clinical Findings

- Poultry worker or parrot fancier
- Atypical pneumonia

Diagnostic Features

- Intracytoplasmic inclusions (no glycogen) in epithelial cells
- Tissue culture
- Serology, complement fixation

Treatment Tetracycline or doxycycline

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10.1.3 *Chlamydophila pneumoniae*

Reservoir/Transmission Humans/respiratory droplets

Pathogenic Features
- Infects smooth muscle, endothelial cells
- May have association with development of atherosclerosis

Clinical Syndrome Atypical pneumonia and bronchitis

Diagnostic Features As for genus

Treatment Tetracycline, erythromycin

10.2 Rickettsiae

▼**Table 3–10.2A** Rickettsiae Species

Disease	Organism	Vector	Reservoir
Rocky Mountain spotted fever	*R. rickettsii*	Tick	Ticks, wild rodents
Rickettsialpox	*R. akari*	Mite	Mites, wild rodents
Scrub typhus	*Orientia tsutsugamushi*	Mites, chiggers	Mites, wild rodents
Epidemic typhus	*R. prowazekii*	Louse	Humans, squirrel fleas, flying squirrels
Murine typhus	*R. typhi*	Flea	Wild rodents
Ehrlichiosis	*Anaplasma phagocytophilum, Ehrlichia chafeensis*	Tick	Small rodents, deer

10.2.1 *Rickettsia rickettsii*

Reservoir/Transmission *Rodents, dogs/tick bite (Dermacentor)*

Pathogenic Features
- Obligate intracellular in endothelial cells of capillaries
- Vasculitis and rash
- Endotoxin may precipitate shock

Clinical Syndrome Rocky Mountain spotted fever (prevalent in Oklahoma, Tennessee, North Carolina, and South Carolina)
- Maculopapular to petechial rash starts on ankles and wrists and spreads to midline
- Palms and soles involved
- Centripetal movement
- Ankle and wrist swelling
- Fever, headache, malaise, myalgia, vomiting, confusion
- Gastrointestinal symptoms, periorbital swelling, conjunctivitis, stiff neck, arthralgia

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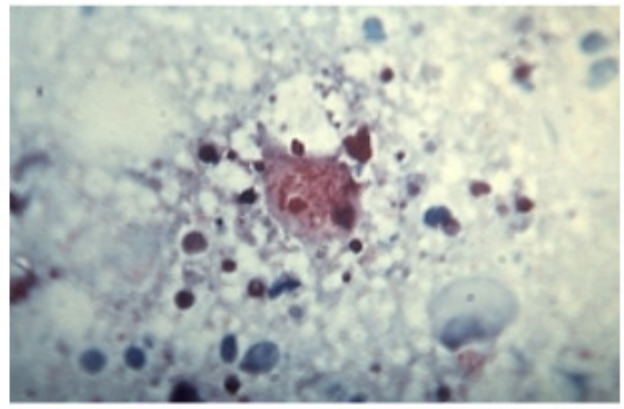
Diagnostic Features

- Clinical, tick bite
- Indirect fluorescent antibody test
- Weil-Felix test (heterophile antibody detected with *Proteus* organisms)

Treatment

- Doxycycline
- Begin therapy without laboratory confirmation

Prevention Avoid tick bite



Science Source

▲ **Figure 3-10.2** *Rickettsia rickettsii*

10.2.2 *Ehrlichia*

▼ **Table 3–10.2B** *Ehrlichia* Species

Organism	Host	Vector	Pathogenesis	Symptoms and Signs	Diagnosis	Treatment
E. chaffeensis	Ticks and deer	*Amblyomma* ticks	Infects monocytes and macrophages	Human monocytic ehrlichiosis similar to RMSF without rash; leukopenia, low platelets, morulae	Indirect FA PCR, blood film with morulae	Doxycycline
Anaplasma phagocytophilum	Ticks, deer, mice	*Ixodes* ticks	Infects neutrophils	Human granulocytic anaplasmosis similar to RMSF without rash; leukopenia, low platelets, morulae	Indirect FA PCR, blood film with morulae	Doxycycline

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11 Mycoplasmataceae

11.1 Family Characteristics

- Non-Gram staining (no cell wall)
- Sterols in membrane
- Smallest extracellular bacterium
- Require cholesterol for culture

11.2 *Mycoplasma pneumoniae*

Reservoir/Transmission Humans/respiratory droplets

Pathogenic Features

- Attachment to cilia and microvilli of bronchial epithelium via P1 protein
- Interference with ciliary action leads to desquamation
- Infiltration with lymphocytes, plasma cells, and macrophages

Clinical Syndrome

- Atypical pneumonia ("walking pneumonia"): Most prevalent form of atypical pneumonia in young adults
- Pharyngitis

Diagnostic Features

- Mulberry-shaped colonies on media containing sterols
- 10 days for growth
- Cold agglutinins (isohemagglutinins which function at 4°C) present in 65% of patients
- EIA and immunofluorescent serological tests

Treatment Erythromycin, tetracycline

11.3 *Ureaplasma urealyticum*

Species Characteristics Urease positive mycoplasmataceae

Reservoir/Transmission Human genital tract/sexual transmission

Pathogenic Features

- Urease allows organism to live in acidic pH
- Sexual activity may promote movement up urinary tract
- Struvite stones/staghorn renal calculi

Clinical Syndrome

- Urethritis
- Prostatitis
- Renal calculi

Diagnostic Features

- Non-Gram staining
- Urease positive

Treatment Tetracycline

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1 Biology of Viruses

1.1 Virus Structure

Viruses are acellular infectious agents that can only replicate inside host cells. They consist of *DNA or RNA* surrounded by structural proteins, and may or may not encode *polymerase enzymes* to complete their life cycle.

1.1.1 Capsids

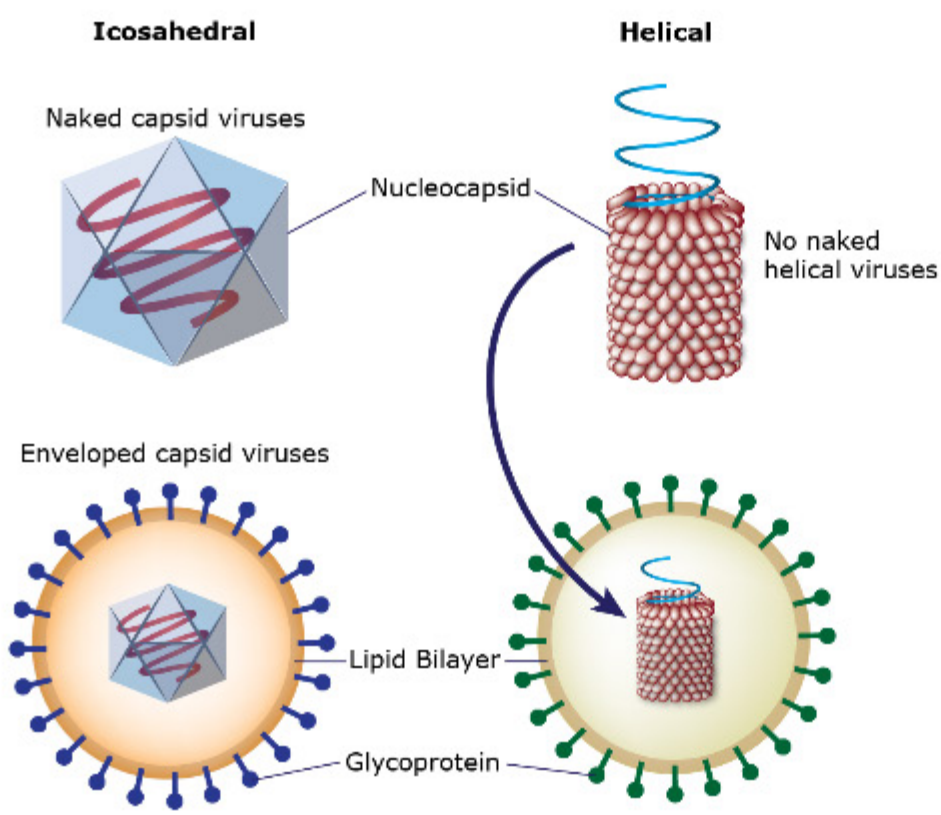
Viruses are divided into two groups:

- **Enveloped Viruses:** These viruses capture membrane from host cells to surround themselves in an envelope. In these viruses the genome protein complex forms the *nucleocapsid* inside the envelope.
- **Naked Viruses:** These viruses have only a protein shell, which is simply referred to as the *capsid*.

Architecturally, capsids and nucleocapsids have two basic shapes:

- **Icosahedral:** Cubic, spherical
- **Helical:** Cylindrical

There are both naked and enveloped icosahedral viruses, but because of the relative fragility of the helical configuration, *all helical viruses must have envelopes*. Protein or glycoprotein projections from the surface of the virus are virus-encoded and important for attachment to host cells.



▲ **Figure 4-1.1A** Viral Morphology

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the anatomy and life cycles of major human virus pathogens.
- Interpret serological findings in the diagnosis of viral hepatitis.
- Describe the diagnosis and treatment of herpes virus infections.
- Explain the life cycle and pathogenesis of human immunodeficiency virus (HIV).
- Distinguish between genetic shift and drift, and describe their roles in viral epidemiology.

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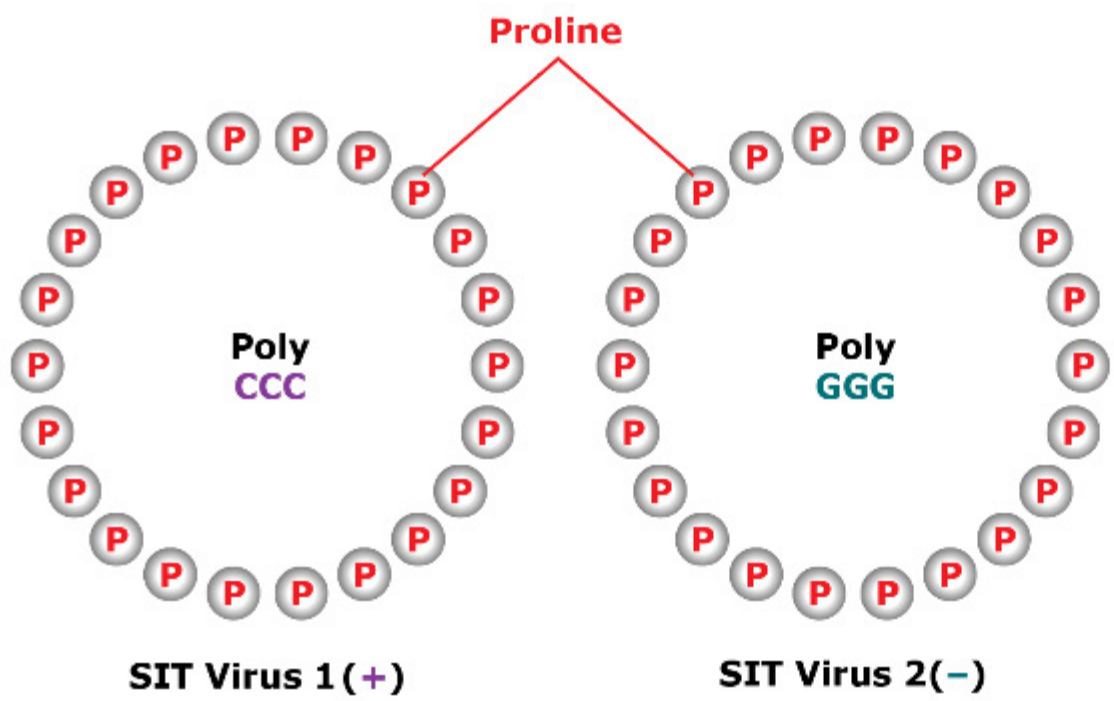
1.1.2 Genomes

Animal viruses may possess genomes made of single- or double-stranded DNA, or single- or double-stranded RNA. RNA viruses are classified into two groups:

- **Positive-Sense RNA Viruses:** These contain an RNA strand that is analogous to eukaryotic mRNA.
- **Negative-Sense RNA Viruses:** These viruses have the strand complementary to mRNA—a strand that does not naturally occur in eukaryotic cells.



▲ **Figure 4-1.1B** Life Cycles of Positive-Sense and Negative-Sense RNA Viruses

To illustrate the difference between positive- and negative-sense RNA virus life cycles, consider the figure above:

- The codon for proline is CCC.
- The codon for glycine is GGG.
- The virus on the left has a CCC genome and a proline capsid—this is the positive-sense RNA virus. Direct translation from the genome creates the viral proteins.
- The virus on the right has a GGG genome, but a proline capsid. The only way to achieve the formation of a proline capsid from a GGG genome is to create the complementary strand of RNA that would read CCC, which could then be translated into the capsid shown. The virus on the right is a negative-sense RNA virus.

Clinical Application

Enveloped viruses are more fragile than naked capsid viruses, so they are relatively easily inactivated by heat, detergents, alcohol, and acids. Naked capsid viruses are much more difficult to destroy, requiring a protein-denaturing agent like chlorine. For this reason, it is more likely that a naked capsid virus will survive passage through gastric acidity. Most viruses that are fecal-oral in transmission belong to the naked capsid category.

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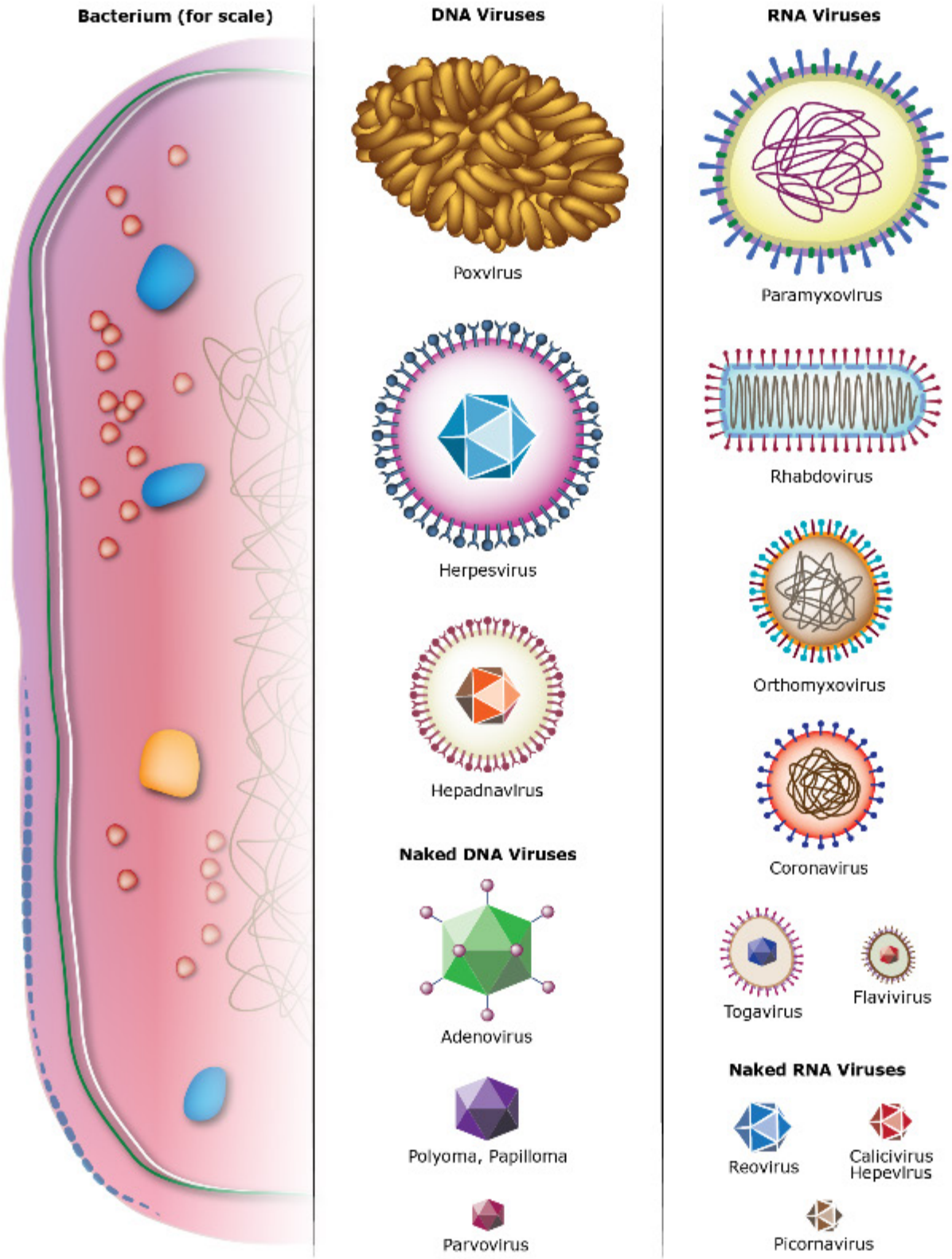
1.1.3 Comparative Virus Shapes and Sizes

Because virus infections are not classically diagnosed by observing the virus—which would generally require electron microscopy—it is not worthwhile to memorize relative sizes. However, it is worth knowing that viruses are orders of magnitude smaller than the smallest bacterium. As a generality, enveloped viruses are larger than naked ones. A few unusual shapes are sometimes mentioned in USMLE vignettes:

- **Poxviruses:** *Brick-shaped* or *complex*
- **Rhabdoviruses:** *Bullet-shaped*
- **Coronaviruses:** Take their name from the shape of the sun's *corona*
- Notice that all naked capsid viruses are smaller than the corresponding enveloped viruses.



▲ **Figure 4-1.1C** Viral Shapes and Sizes

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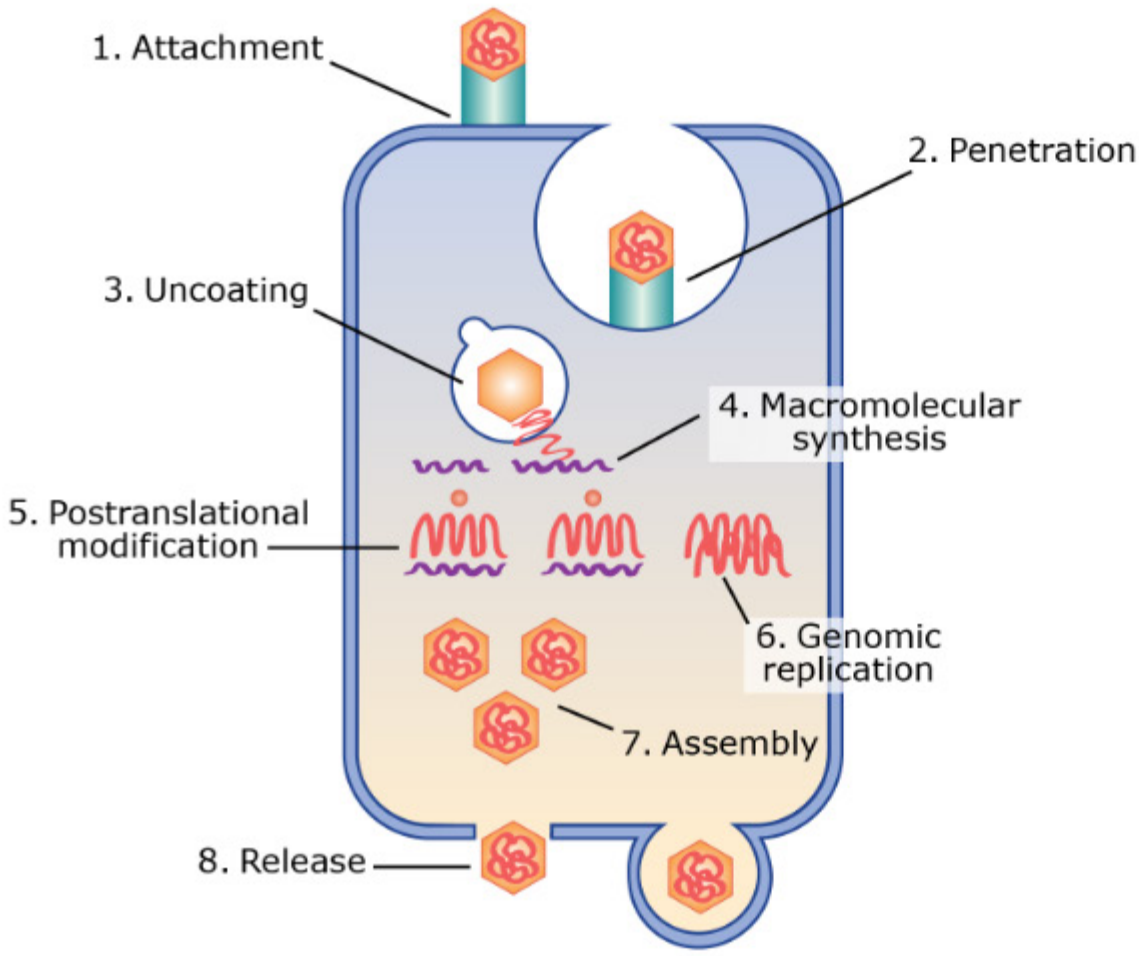
1.2 The Generalized Virus Life Cycle



▲ **Figure 4-1.2A** Viral Life Cycle

1.2.1 Spread of Viruses

Viruses are spread by the same mechanisms used by all microbes: Airborne droplets, fecal-oral contamination, sexual or parenteral means, etc. When viruses are spread by arthropod vectors they are said to be *arboviruses*, a designation that is an acronym for "*ar*thropod *bo*rne" which has no relationship to the taxonomy of the agent.

1.2.2 Attachment

Viruses attach to host cells by interaction with specific host cell receptors. This interaction defines the virus' *tropism* or *host range* (its choice of target cell). For enveloped viruses, it is viral proteins embedded in the envelope that attach to host cell receptors. In the case of naked capsid viruses, virus-encoded capsid proteins serve this purpose.

A few specific virus/receptor interactions may be tested. These include:

- **Cytomegalovirus and Herpes Simplex:** Heparan sulfate
- **Epstein-Barr Virus:** CD21
- **HIV:** CD4 and either CXCR4 or CCR5
- **Parvovirus:** Erythrocyte P antigen
- **Rabies:** Acetylcholine receptor
- **Rhinovirus:** ICAM-1

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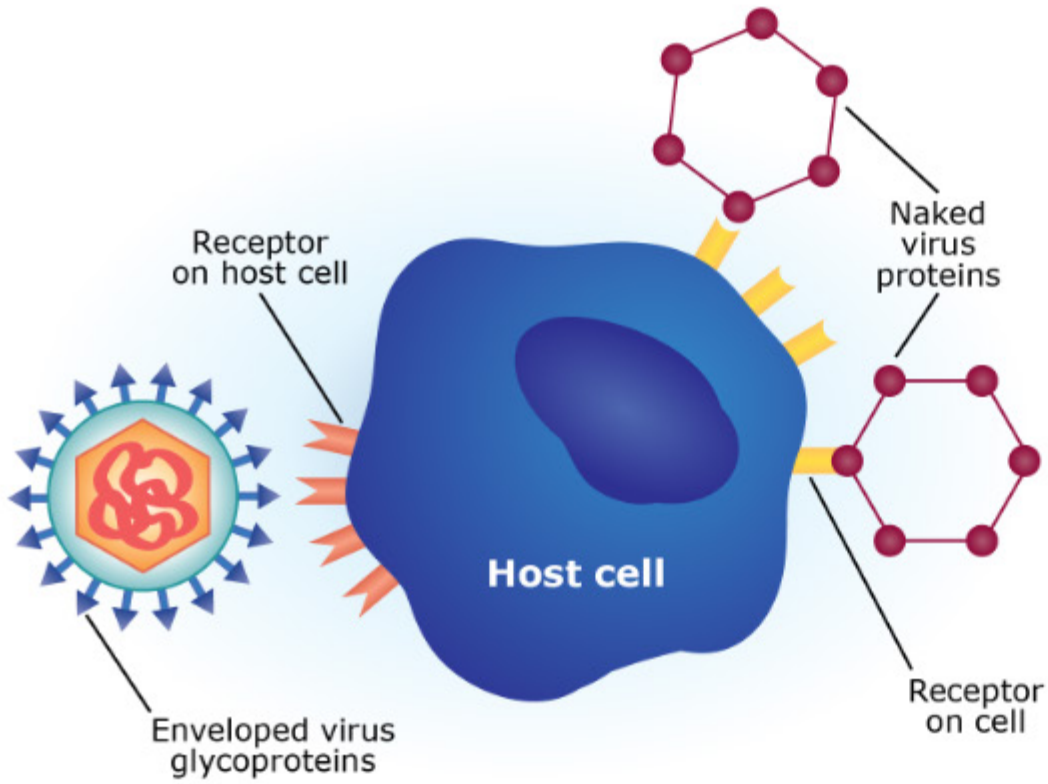


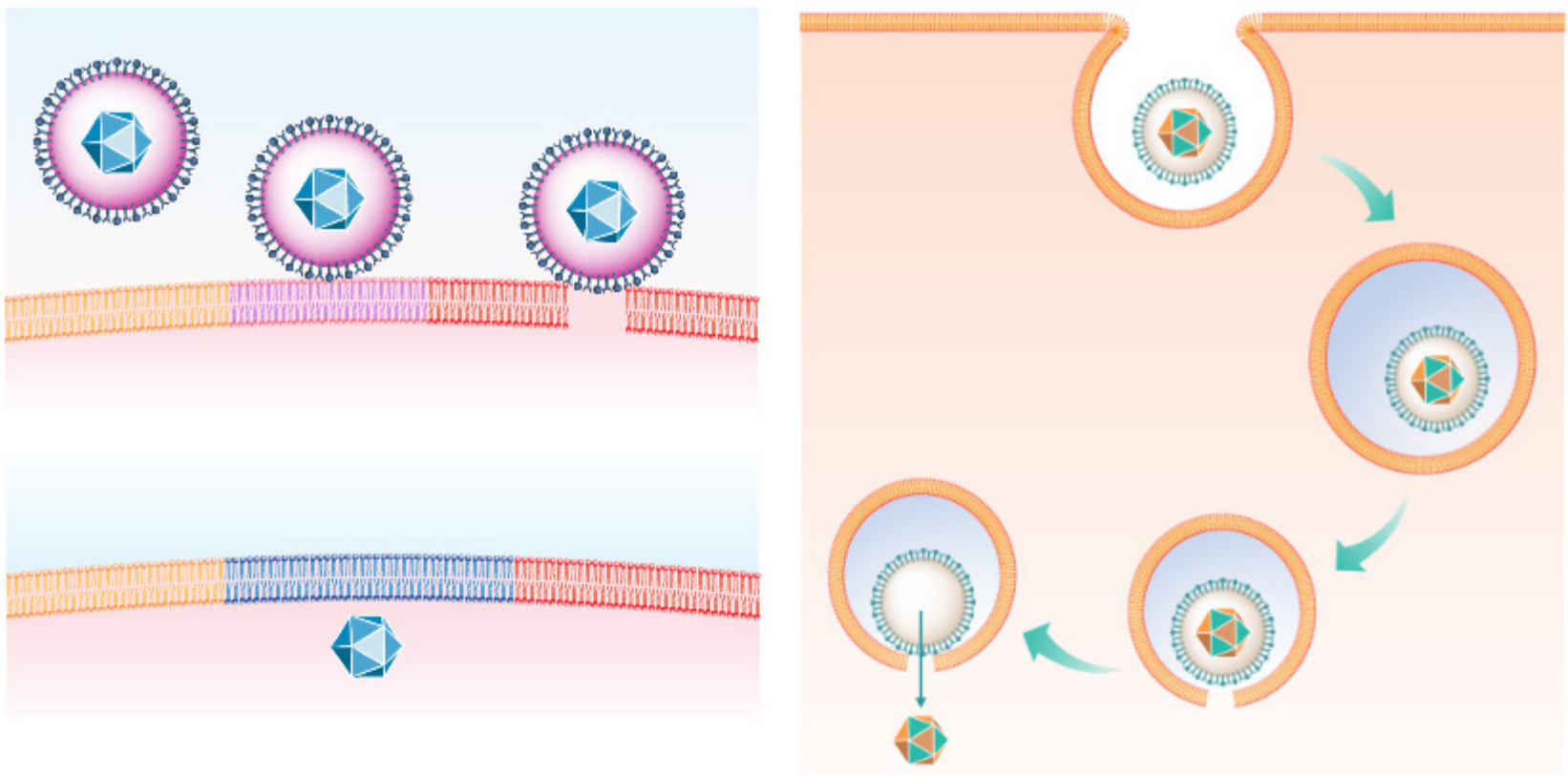
▲ **Figure 4-1.2B** Viral Attachment

1.2.3 Penetration

Enveloped viruses enter cells in one of two ways:

- **Direct Fusion:** Viral envelope fuses with the cellular membrane, discharging the nucleocapsid directly into the cell.
- **Viropexis:** Virus penetrates via receptor-mediated endocytosis and production of an endosomal vesicle.

Naked capsid viruses only can enter the cell by viropexis.



▲ **Figure 4-1.2C** Direct Fusion (*left*) and Viropexis (*right*)

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Clinical Application

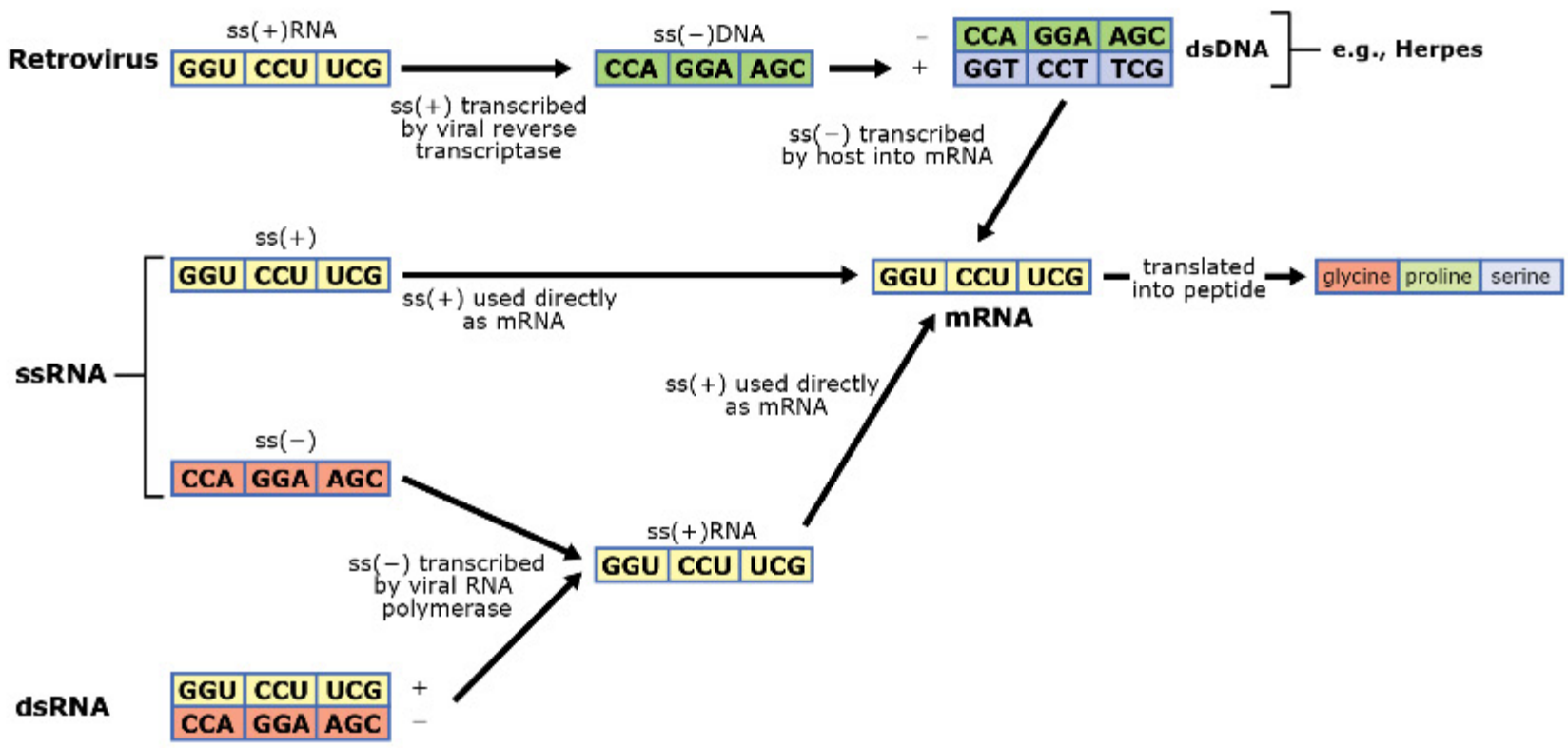
Viruses that enter cells via direct fusion leave viral glycoproteins on the surface of the cell. This results in the tendency for infected cells to fuse with neighboring cells, and causes formation of *syncytia* (multi-nucleated giant cells), which can be both diagnostic and important in the protection of the virus from humoral immune responses. The classic syncytial viruses are the paramyxoviridae, the herpesviridae, and HIV.

1.2.4 Uncoating

Nucleocapsids of viruses that enter cells via direct fusion are discharged directly into the cytoplasm. Viruses that are enclosed in an endosomal vesicle are released by fusing viral membrane with endosomal membrane. Some viruses use fusion with lysosomes to release the nucleocapsid.

1.2.5 Synthesis of Macromolecules

The next step of the viral life cycle is to make mRNA and begin to produce early proteins. The process is different for different viruses depending on the genomic message. Most RNA viruses perform this step in the cytoplasm, whereas most DNA viruses travel to the nucleus to make mRNA. Immediate early or early proteins are needed to shut down the activities of the host cell and replicate the genome. Later proteins will serve as the building blocks of a virus' progeny.



▲ **Figure 4-1.2D** Viral mRNA Synthesis

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1.2.6 Genomic Replication

A virus now must make multiple copies of its genome. Again, most RNA viruses perform this process in the cytoplasm using RNA-dependent RNA polymerases that they either carry into or produce inside the cell. Most DNA viruses perform this process in the nucleus, either with their own DNA-dependent DNA polymerases or with those of the cell they induce to remain in the S phase of the cell cycle.

▼ **Table 4–1.2** Viral Genomic Replication

Virus Category	Family	Parental Genome	Replicative Intermediate	Progeny Genome
DNA	Most	dsDNA	Semi-conservative replication	dsDNA
	Hepadnavirus	dsDNA	ss(+)RNA	dsDNA
+RNA	Most	+RNA	-RNA	+RNA
	Retrovirus	+RNA	dsDNA	+RNA
-RNA	All	-RNA	+RNA	-RNA

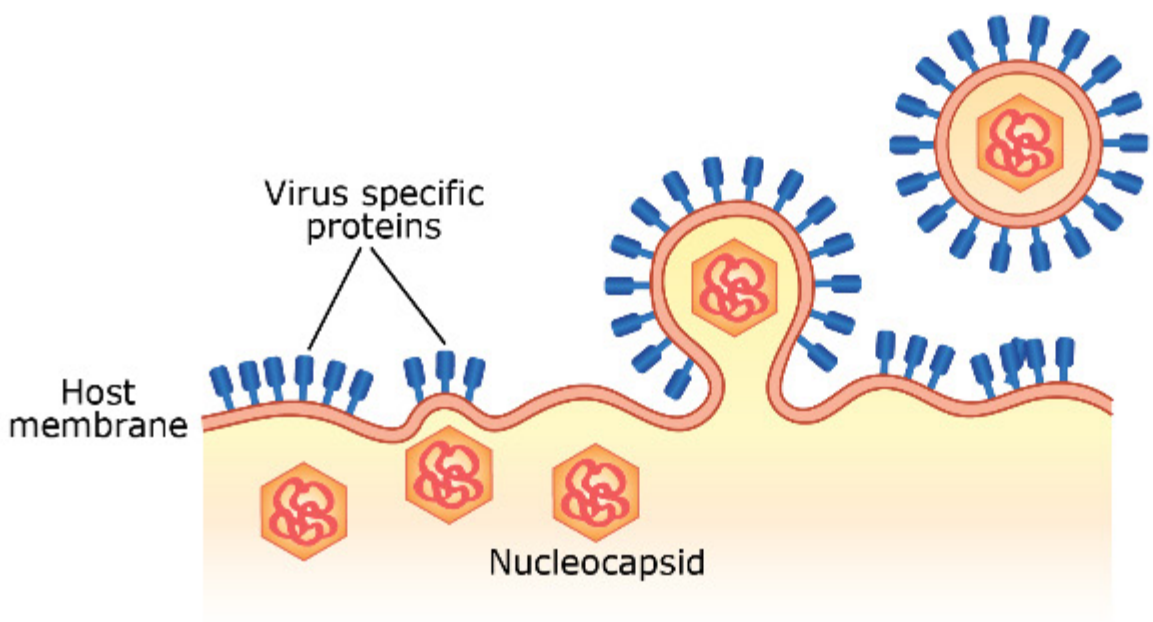
Highlighted fields indicate steps at which reverse transcription is required.

1.2.7 Assembly

The individual component parts—enzymes, nucleic acid strands, and proteins—are assembled into the next generation of virions.

1.2.8 Release

Most naked capsid viruses leave a host cell by causing cellular lysis. Most enveloped viruses will bud off the surface of the cell, capturing surrounding membrane as they leave.



▲ **Figure 4-1.2E** Viral Release

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1.3 Outcomes of Virus Infection

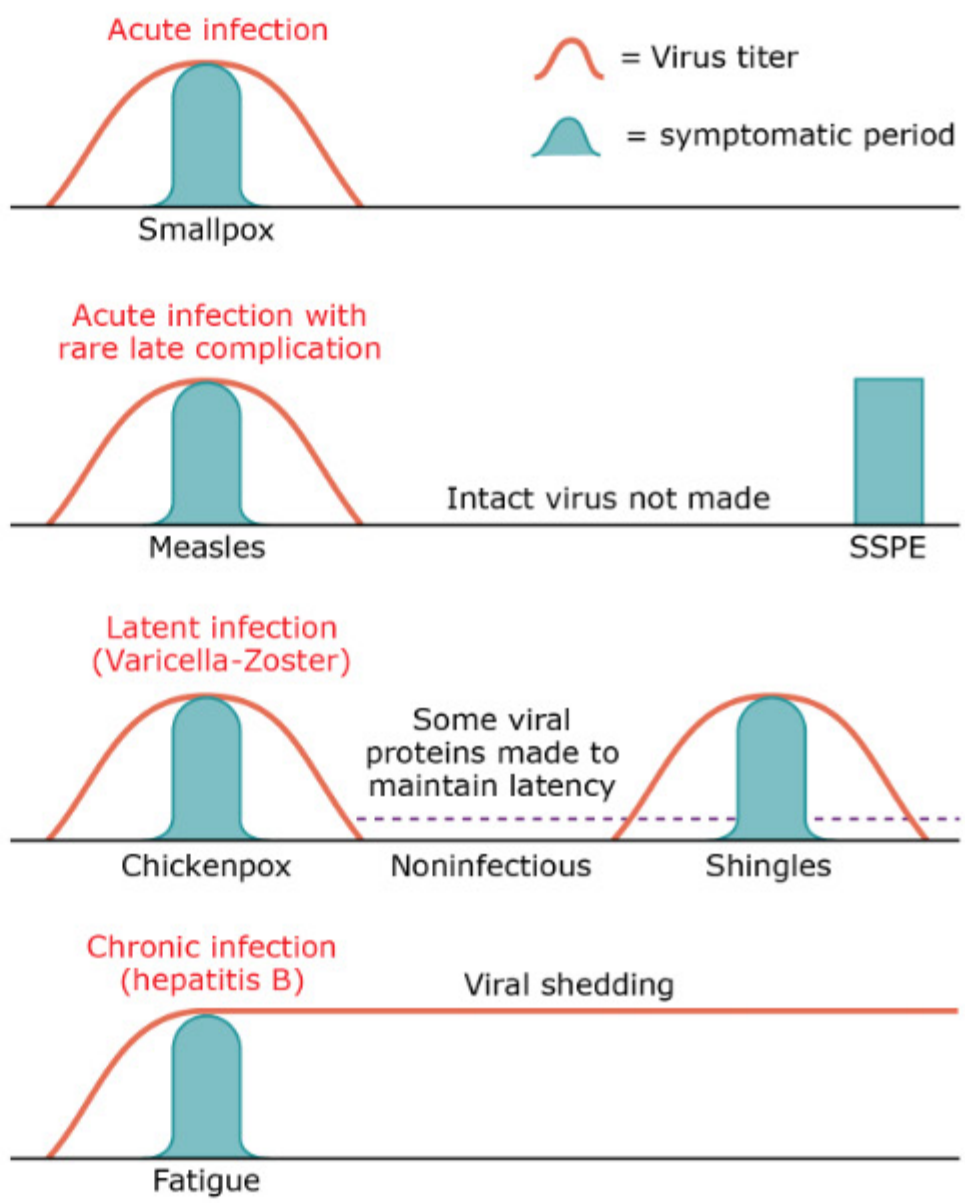
1.3.1 Cellular Level

Viral infections have a variety of effects at the cellular level:

- **Abortive Infections:** These produce no viral progeny and the cell is unaffected.
- **Cytolytic Infections:** These result in the lysis of the cell during the production of progeny.
- **Persistent Infections:** These result in one of three outcomes:
  - **Productive,** in which case progeny are produced and the cell is prematurely aged.
  - **Latent,** in which case progeny are not produced and there is no overt damage to the cell.
  - **Transforming,** in which, with or without progeny production, the cell becomes immortalized.

1.3.2 Organismal Level

Most virus infections follow a pattern in which viral shedding occurs before, during, and after the symptomatic period. Although the symptoms for a given virus vary depending on tissue tropism and virulence, this means the patient will be contagious before symptoms begin and after they have subsided. In viruses that exhibit latency, there will be a period when no infectious particles are being made and the infection is asymptomatic, followed by a reactivational outbreak in which virus is again shed.



▲ **Figure 4-1.3A** Courses of Viral Infection

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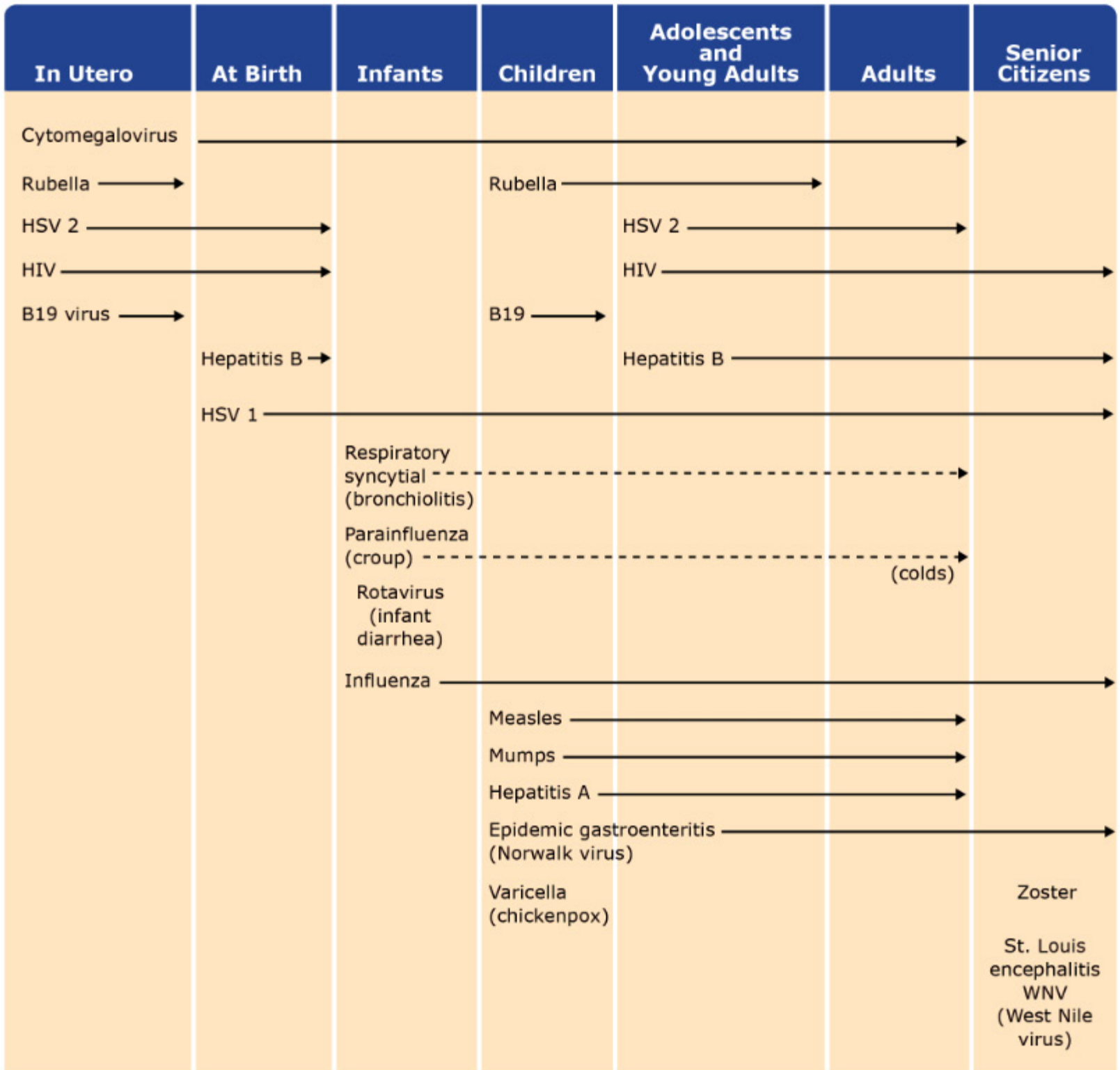
Age Groups Most Commonly Presenting With Viral Infection Although many viruses cause symptomatic infections purely based on exposure, in some cases the age of the patient is a useful clue toward a specific diagnosis. The following figure shows the most classic age groups affected by particular viral infections.



▲ **Figure 4-1.3B** Viral Infections: Age Most Commonly Infected

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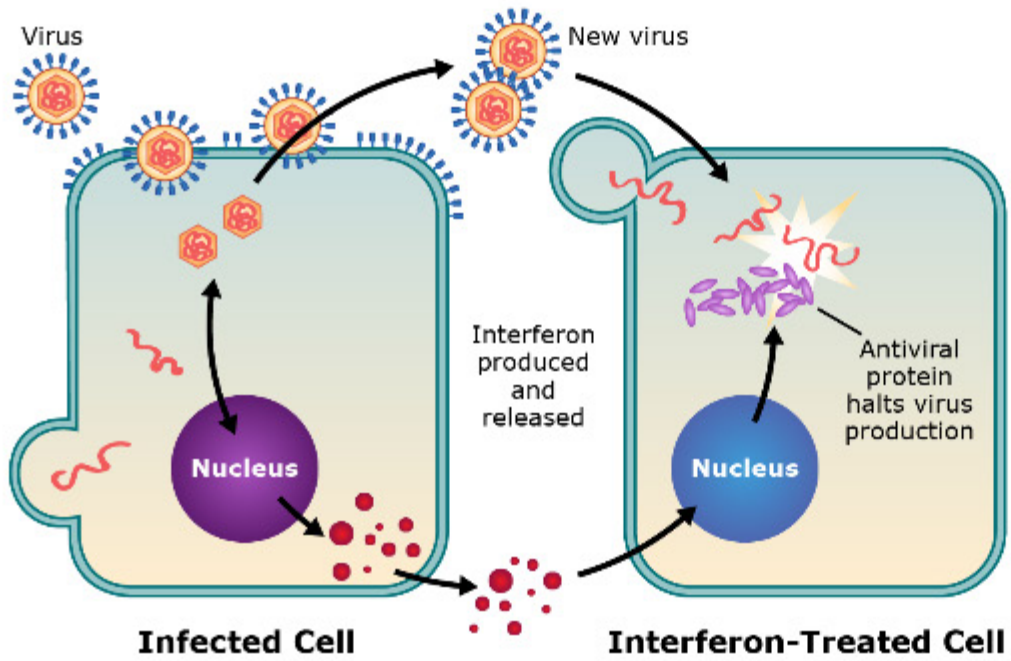
Immune Responses to Viruses Because viruses are obligate intracellular pathogens, the most important protective immune responses against them are cell-mediated. When antibodies are produced against viruses, they will have efficacy only against viral particles before they attach to cells.

Type 1 interferons are important innate immune responses to viral infection. These molecules, IFN-α and IFN-β, are:

- Not virus-specific
- Produced by virus-infected cells
- Inhibit viral protein synthesis in nearby cells by
  - Activation of an RNA endonuclease
  - Activation of a protein kinase that then inactivates eIF2



▲ **Figure 4-1.3C** Interferon Production

1.4 Viral Genetics

Viruses are capable of rapid evolution to respond to their environments through the mechanisms of mutation and recombination. Human viruses have extremely high rates of mutation that produce large numbers of defective particles, but also allow them to respond to the host immune response by the creation of resistant variants.

1.4.1 Mutation

Most DNA viruses use the DNA synthetic machinery of their host cell and benefit from the proofreading and error-correcting mechanisms that are built into those systems. The larger DNA viruses (adenovirus, herpesvirus, poxvirus) encode their own DNA polymerases, which are more error prone than those of their eukaryotic counterparts.

RNA virus replication is fraught with even more mutation, because viral RNA polymerases possess no proofreading capacity. This provides this group of viruses with impressive genetic plasticity to evolve successful strains in the face of changing environmental pressures. The origination of genetic variants due to mutational change is referred to as *antigenic drift*.

Clinical Application

Both type 1 (IFN-α and IFN-β) and type 2 interferons (IFN-γ) are now in clinical use to treat a variety of diseases. All interferons increase expression of class 1 and class 2 MHC molecules and stimulate NK cells. Their production, along with that of most other important immunological cytokines, is under the control of transcription factor NFκB.

Specific therapies include:

- **IFN-α**: Hepatitis B and C, hairy B cell leukemia, Kaposi sarcoma, chronic myelogenous leukemia.
- **IFN-β**: Increases the length of remissions in multiple sclerosis.
- **IFN-γ**: Chronic granulomatous disease.

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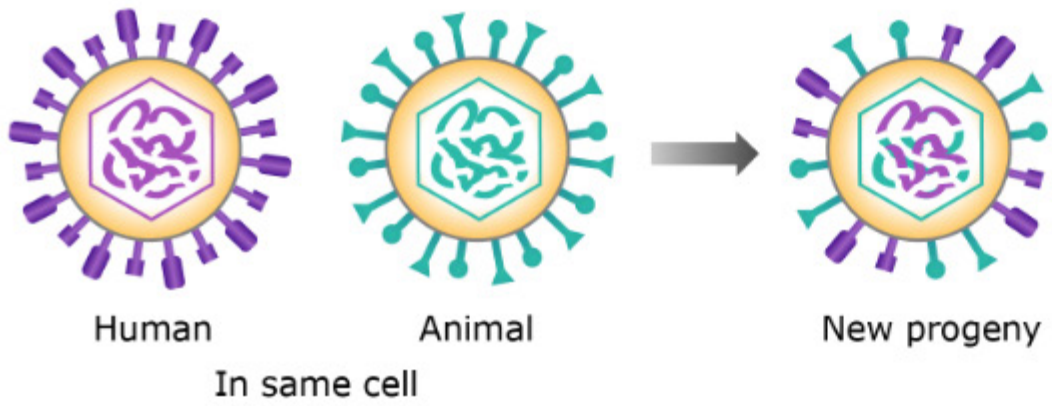
1.4.2 Recombination and Reassortment

Homologous recombination between variants of one type of DNA virus is possible using enzymes available within cells, but cells do not possess the machinery for recombination of RNA molecules. However, in viruses with segmented genomes (reovirus, orthomyxovirus, bunyavirus, and arenavirus), accidental *reassortment* of segments of the genome can result in the appearance of dramatically changed variants. This is known as *genetic shift*, and is responsible for *pandemics* of disease because the host population does not have immunity to the new, dramatically different variant strain.

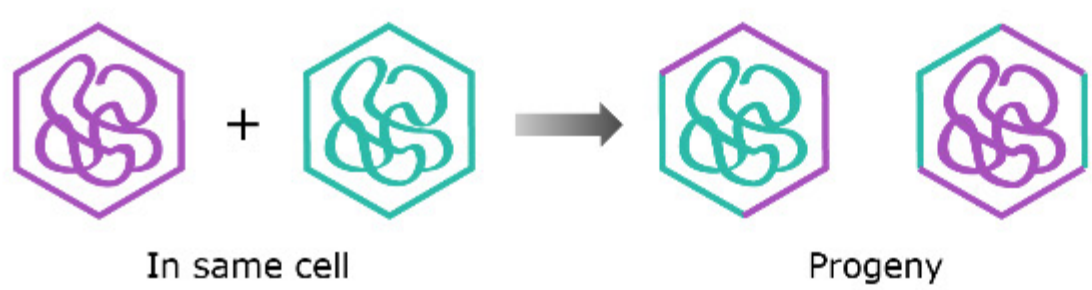


▲ **Figure 4-1.4A** Antigenic Shift

Nonsegmented RNA viruses also may undergo recombination by a *"copy choice" mechanism*. If the RNA replicase dissociates from one RNA template and resumes copying at the same spot on another template, then progeny can be created that have information from two RNA molecules. In retroviruses, the diploid genome appears ready-made for this form of recombination during reverse transcription.

1.4.3 Phenotypic Mixing

When two related viruses infect one cell, it is possible for the capsid proteins of the progeny generation to mix proteins from each of the parental viruses. This is called *phenotypic mixing*, and because capsid proteins dictate tropism, it may result in altered cellular infection for one generation.



▲ **Figure 4-1.4B** Phenotypic Mixing

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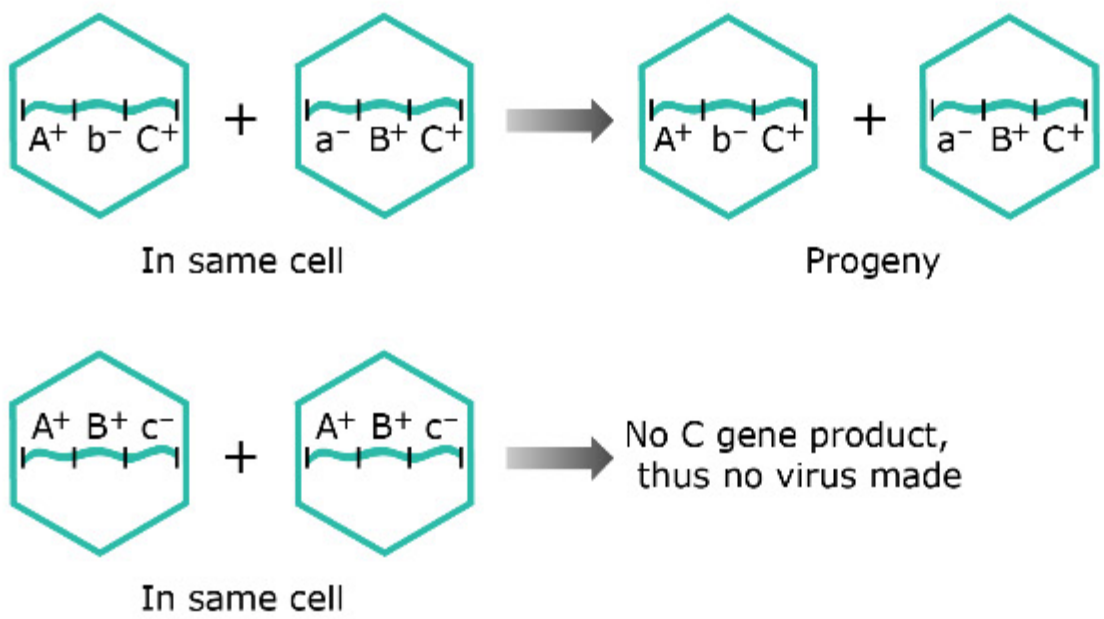
1.4.4 Phenotypic Masking

When two related viruses infect one cell, and the capsid proteins of one parental virus form around the genome of the other, the progeny generation may again express different cellular tropism from the parental viruses. This is referred to as *phenotypic masking*.

▲ **Figure 4-1.4C** Phenotypic Masking

1.4.5 Complementation

When two related, defective viruses infect one cell, progeny viruses can be produced as long as their defects are in different genes, because they can *"complement"* one another by sharing gene products. However, if both defective viruses lack the same essential gene product, no viral progeny are formed and the result is abortive infection.



▲ **Figure 4-1.4D** Complementation

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1.5 Mechanisms of Viral Oncogenesis

Normal cellular growth is a tightly regulated interaction between positive molecular signals for cell division (cellular *proto-oncogene* products) and mechanisms that stop the cell cycle so DNA repair can be undertaken (*anti-oncogenes* or *tumor suppressor genes*). There are a number of viral infections that upset this delicate balance.

▼ **Table 4–1.5** Viral Oncogenesis

Genome	Virus	Malignancy	Molecular Basis
DNA	**Epstein-Barr virus**	Burkitt lymphoma	Acts as polyclonal B cell mitogen and sets the stage for the acquisition of the t(8:14) translocation and other mutations.
		B cell lymphomas	Latent membrane protein-1 (LMP-1) gene activates NFκB and JAK/STAT pathways and prevents apoptosis by activating Bcl2. EBNA-2 activates cyclin D and *src* family of proto-oncogenes.
	Hepatitis B virus	Hepatocellular carcinoma	Activation of NFκB pathway in hepatocytes in response to mediators from activated immune cells. This blocks apoptosis, allowing accumulation of mutations.
	Human Papilloma-virus, serotypes 16, 18 (high-risk HPV types tend to integrate into chromosomes; in cancers, genomes are found integrated)	Squamous cell carcinoma of the cervix and penis	E7 protein binds to RB protein, and inactivates p21 and p27 (tumor suppressors) and activates cyclins E and A. E6 protein binds p53 to target it for degradation, inhibits BAX's pro-apoptotic signals, and activates telomerase to combat cellular senescence.
RNA	**HTLV-1**	T cell leukemia	The *tax* gene product activates transcription of the viral genome, transactivates the cellular genes for IL-2 and IL-2 receptor, inactivates cell cycle inhibitor p16/INK4a, and enhances cyclin D activation. It also activates NFκB.
	Hepatitis C virus	Hepatocellular carcinoma	Chronic liver cell injury and compensatory regeneration. Activation of NFκB pathway in hepatocytes in response to mediators from activated immune cells. This blocks apoptosis, allowing accumulation of mutations.

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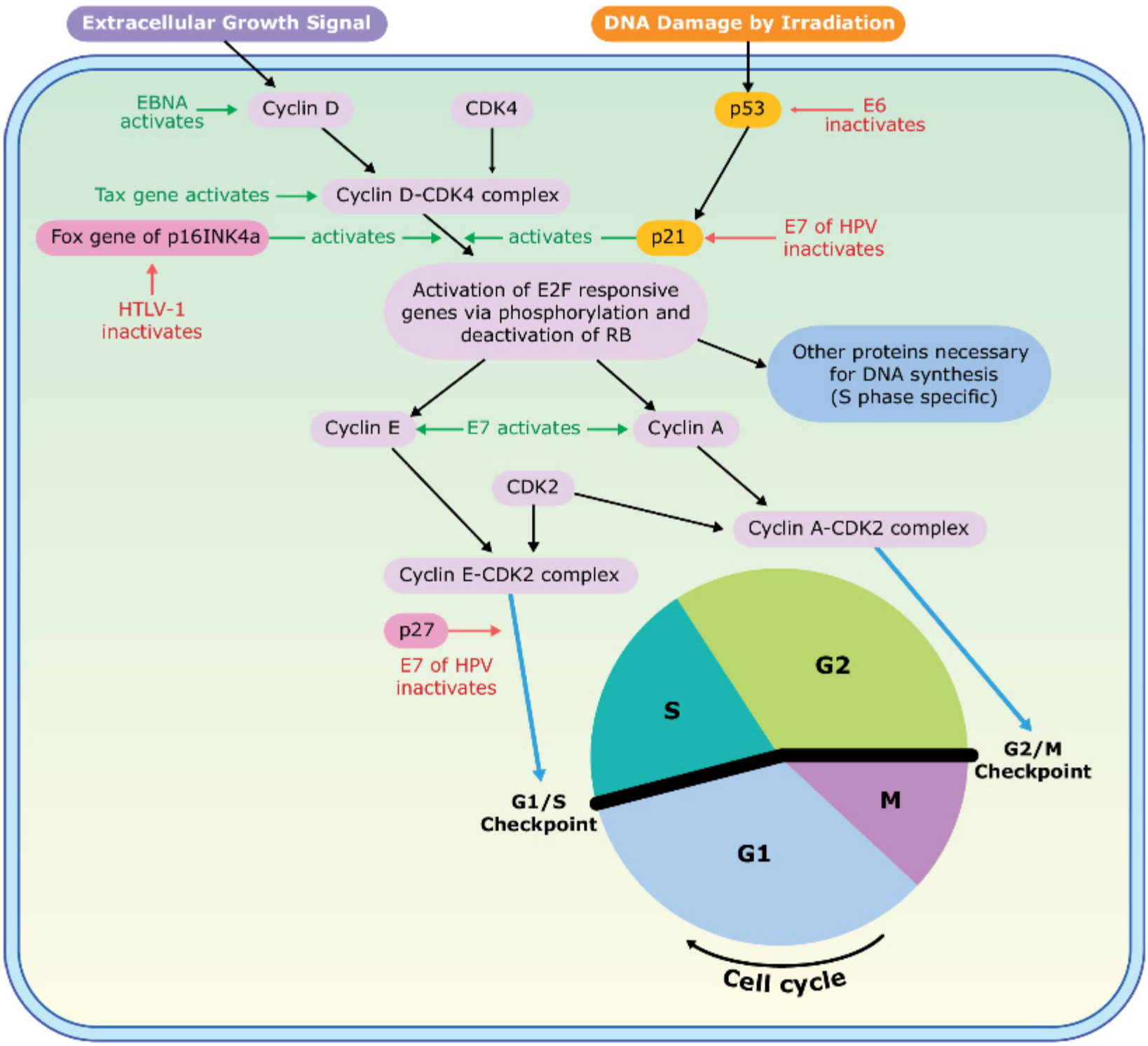

CDK = Cyclin-Dependent Kinase

▲ **Figure 4-1.5** Viral Oncogenesis and Cell Cycle Regulation

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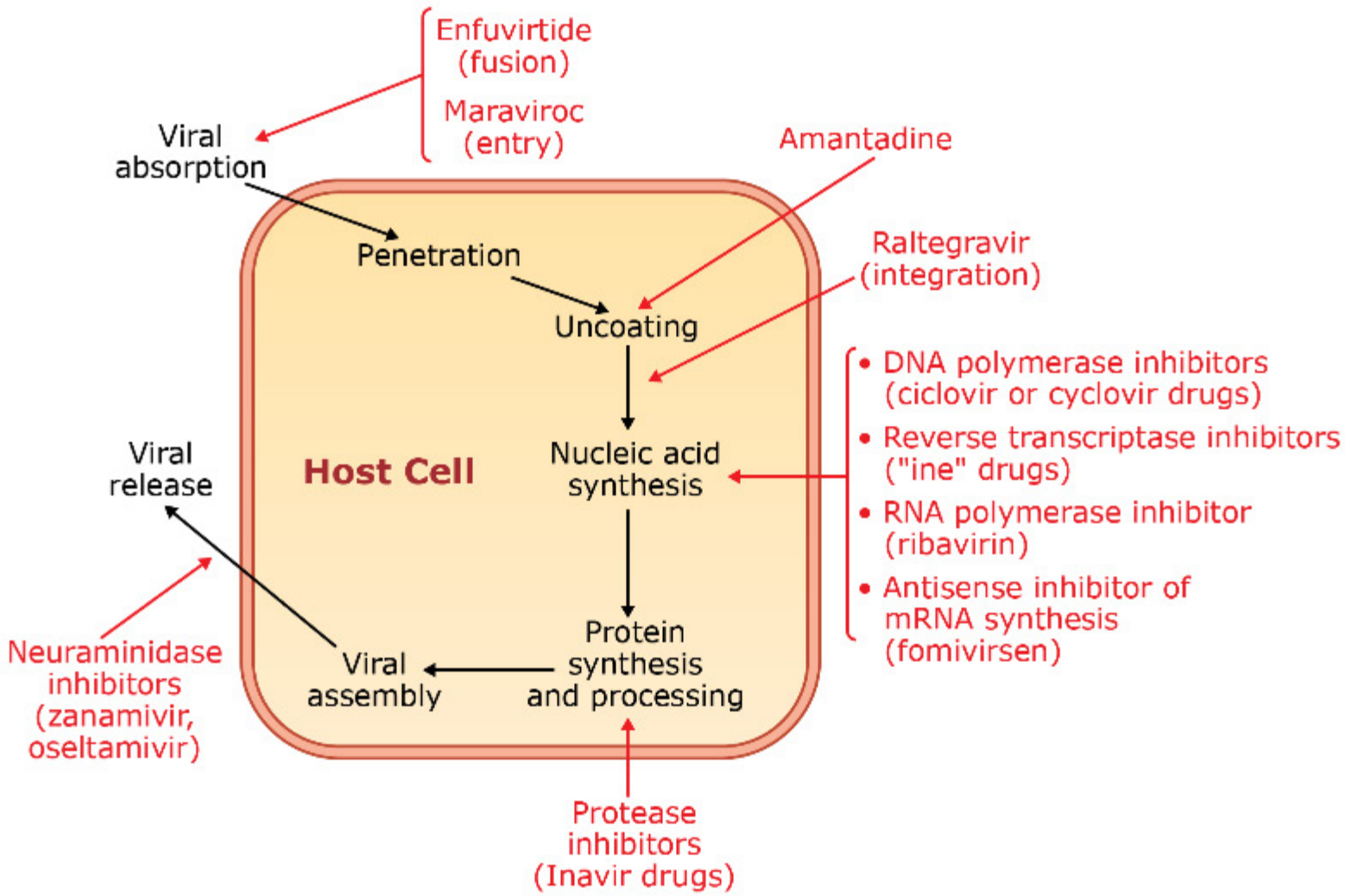
1.6 Antiviral Drugs

There are fewer drug therapies for viruses than for bacteria and, due to the high rate of viral mutation, resistances emerge quickly and must be carefully monitored. The generalities of viral modes of inhibition are shown here.



▲ **Figure 4-1.6** Mechanism of Action of Antiviral Drugs

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2 Hepatotropic Viruses

2.1 Distinguishing Characteristics

The symptoms of viral hepatitis are similar regardless of the viral etiology: Fatigue, loss of appetite, nausea, pain and fullness in the right epigastric region, clay-colored stools, darkening of urine, and jaundice. It is important to distinguish between these agents serologically to evaluate prognosis and predict sequelae of infection.

▼ **Table 4–2.1** Overview of Hepatotropic Viruses

Name	Family and Morphology	Transmission	Clinical	Treatment	Diagnosis
Hepatitis A	Picornavirus ss(+)RNA, naked, icosahedral	Fecal-oral	Acute viral hepatitis, no chronicity	• Pooled immunoglobulins • Supportive care, killed vaccine	Anti-HAV IgM = Active disease
Hepatitis B	Hepadnavirus Partially dsDNA, circular, enveloped, icosahedral, carries DNA polymerase (reverse transcriptase) enzyme	Sexual, parenteral	• Acute, fulminant, or chronic hepatitis • 10% chronicity adults, 90% infants • Primary hepatocellular carcinoma, cirrhosis • Liver injury due to cell-mediated immunity	• Supportive for acute infection, chronic cases may respond to α-IFN and lamivudine • Prevention: Recombinant DNA vaccine contains HBsAg; blood- and organ-donor screening	HBsAg plus IgM anti-HBcAg
Hepatitis C	Flavivirus ss(+)RNA, enveloped, icosahedral	Sexual, parenteral	• Anicteric or asymptomatic acute infection, 85% chronicity • No. 1 infectious cause of chronic liver disease and liver transplantation • Cirrhosis, primary hepatocellular carcinoma	• α-IFN, ribavirin • Prevention: Vaccine unlikely because of genomic mutability	EIA and Western blot for anti-HCV antibodies, often negative for up to 4 months
Hepatitis D	Defective, circular ssRNA virus with HBsAg envelope	Sexual, parenteral	• **Coinfection:** HBV and HDV are acquired at the same time; no greater risk of severity than hepatitis B alone • **Superinfection**: HDV infects a patient during chronic hepatitis B: high risk of severe disease • **Complications:** Fulminant hepatitis, cirrhosis	• IFN-alpha and lamivudine • Prevention: Hepatitis B vaccine	HbsAg plus anti-HDV
Hepatitis E	Hepevirus ss(+)RNA, naked, icosahedral	Fecal-oral	• Acute, not chronic • Epidemics in Asia, Africa • 20% mortality in pregnant women	Supportive	Serology

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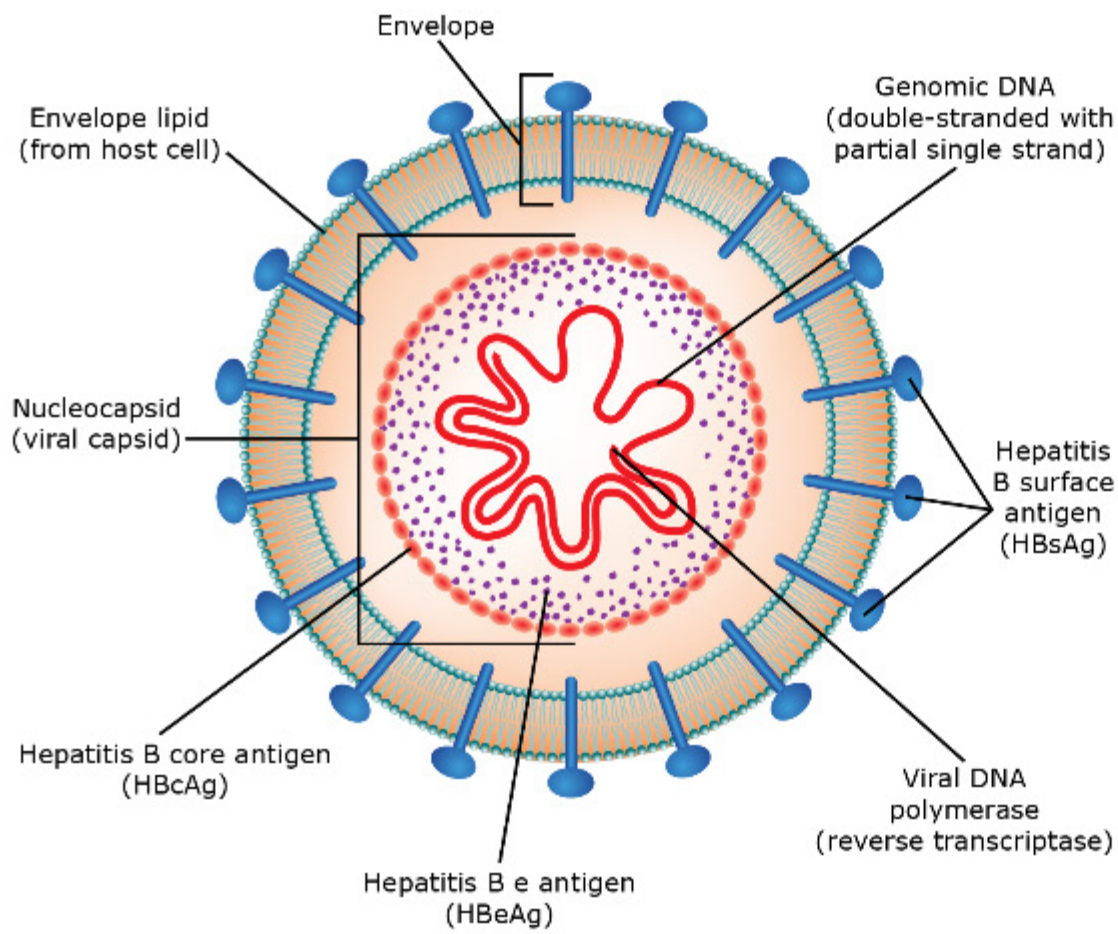
2.2 Hepatitis B Structure

The complete virion (the Dane particle) is made of the following components:

- **HBsAg:** The surface antigen of the virus.
- **HBcAg:** The main core antigen.
- **HBeAg:** A second core antigen, a low-molecular weight glycoprotein secreted from infected cells.
- **DNA Polymerase:** Reverse transcriptase.
- **HBx Protein:** Transcription activator.



▲ **Figure 4-2.2** Complete Infectious Virion (Dane Particle)

2.3 Hepatitis B Serology

Evaluation of patient status and prognosis is done by analysis of viral antigens and antibodies in the serum:

- **HBcAb:** The first antibody to appear, it is used as the diagnostic antibody. It will be IgM in isotype first, and then switch to IgG.
- **HBeAg:** This antibody is used as a measure of how contagious the patient is. If there is an excess of HBeAg in the blood, it correlates with virus shedding. If by contrast the patient has begun to make HBeAb, the case is less contagious.
- **HBsAg:** It is used as the measure of active infection. If it persists in the blood past six months postinfection, the case is defined as chronic.
- **HBsAb:** It is the only antibody that provides protective immunity. Its production is heralded by a *"window period"* when the HBsAg will disappear from the blood, before a rising titer of HBsAb can be measured.

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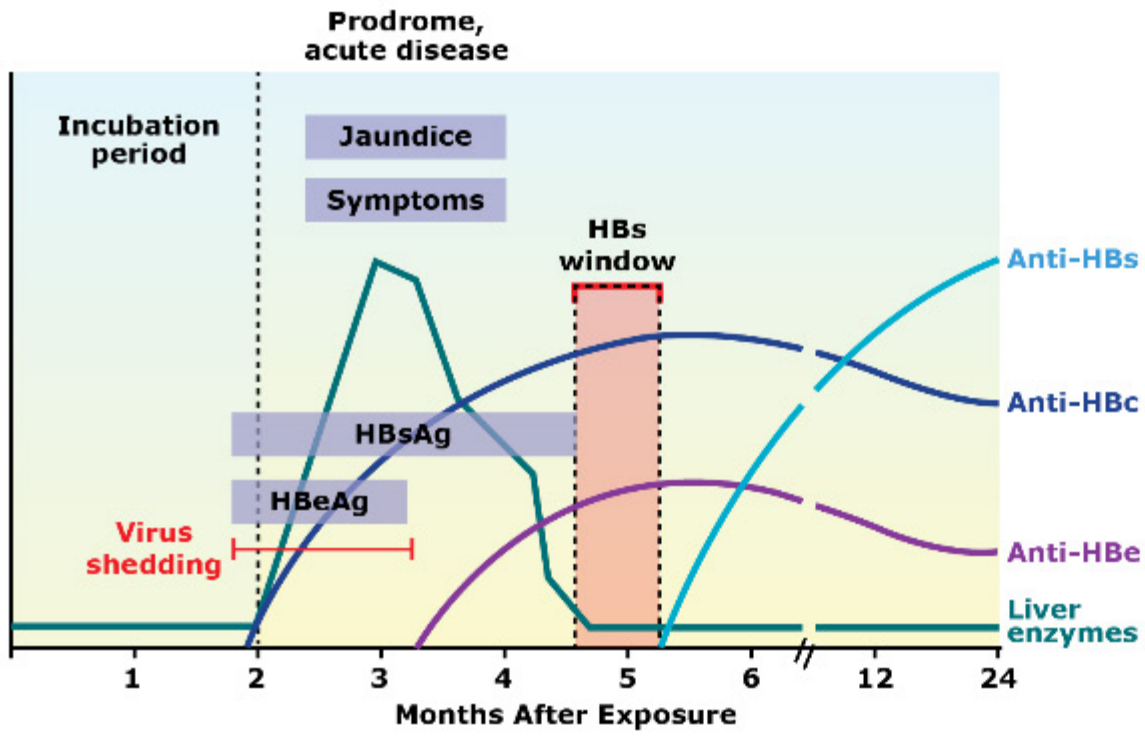
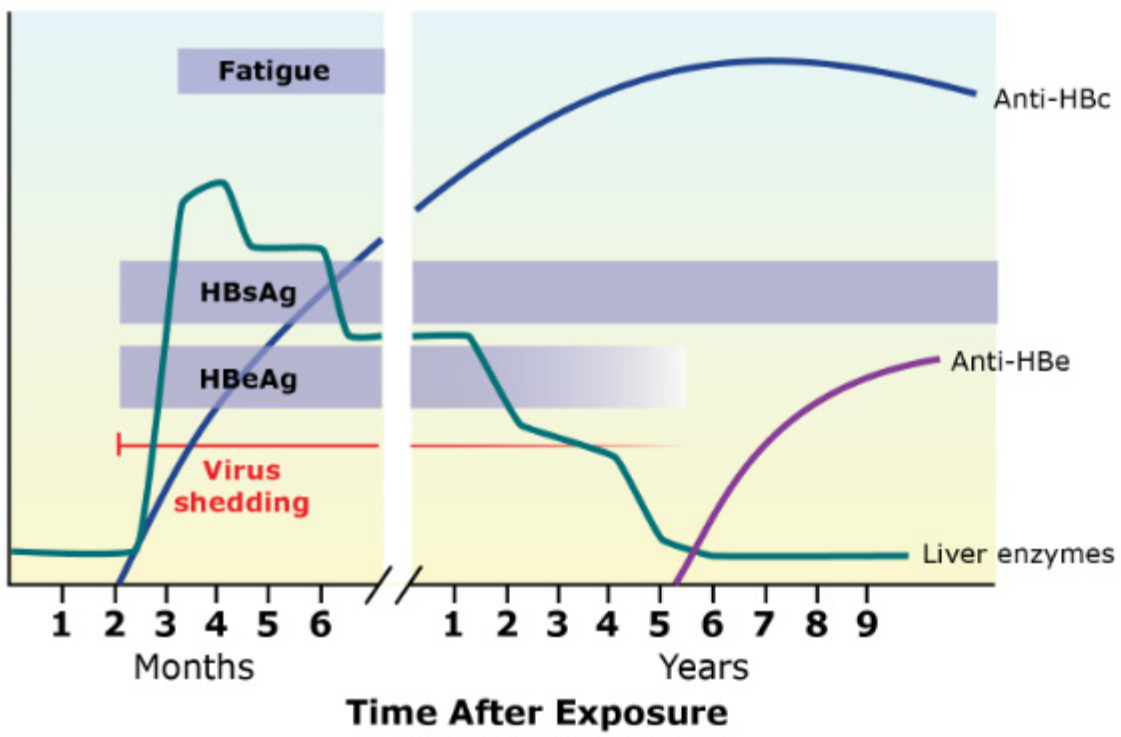
2.3.1 Acute Infection



▲ **Figure 4-2.3A** Acute Hepatitis B Serology

2.3.2 Chronic Infection



▲ **Figure 4-2.3B** Chronic Hepatitis B Serology

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2.3.3 Summary of Serologic Diagnosis

The following table of serological results is for all possible patient cases that can be asked on the exam. Notice that acute and chronic hepatitis B may look exactly the same serologically, and these can be distinguished only by the time that has transpired postexposure. *Chronic active hepatitis* is associated with the continued presence of the HBeAg and these patients are highly contagious. *Chronic persistent hepatitis* is associated with the development of HBeAb, and these individuals are less contagious to others.

▼ **Table 4–2.3** Serologic Diagnosis of Hepatitis

Serological Marker	Acute < 3 Months	Acute 3-6 Months	Window Period	Acute Recovering	Chronic	Vaccinated
HBcAg	–	–	–	–	–	–
HBcAb	+	+	+	+	+	–
HBeAg	+	–	–	–	+/–	–
HBeAb	–	+	+	+	–/+	–
HBsAg	+	+	–	–	+	–
HBsAb	–	–	–	+	–	+

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3 DNA Viruses

3.1 Summary of Characteristics

DNA viruses:

- Are double-stranded, except parvovirus.
- Replicate in the nucleus (create intranuclear inclusion bodies), except poxvirus.
- Are icosahedral, except poxvirus.

3.2 DNA Virus Families

▼ **Table 4–3.2** DNA Virus Families

Virus Family	DNA Type	Virion Carries Polymerase	Envelope	Site of DNA Replication	Major Viruses
Parvovirus	ssDNA	No	Naked	Nucleus	B19 (fifth disease)
Papillomavirus	dsDNA circular	No	Naked	Nucleus	HPV
Polyomavirus	dsDNA circular	No	Naked	Nucleus	JC, BK
Adenovirus	dsDNA linear	No	Naked	Nucleus	Adenovirus
Hepadnavirus	Partial dsDNA circular	Yes[1]	Envelope	Nucleus, RNA intermediate	Hepatitis B
Herpesvirus	dsDNA linear	No[2]	Envelope (nuclear)	Nucleus: Virus assembles in the nucleus	HSV, Varicella-Zoster, EBV, CMV, HHV6–8
Poxvirus	dsDNA linear	Yes[3]	Envelope	Cytoplasm	Variola (virus), Vaccinia (vaccine), Molluscum contagiosum

1. Hepadnavirus carries a DNA polymerase that has RNA-dependent DNA polymerase, DNA-dependent DNA polymerase, and RNase H activities (reverse transcriptase).
2. The herpesvirus genome encodes two early proteins: A DNA polymerase and a thymidine kinase involved in DNA replication. Both of these are important targets of antiviral chemotherapy, but they are not carried with the virus into the cell.
3. Poxvirus carries a DNA-dependent RNA polymerase with it into the cell since it intends to replicate DNA in the cytoplasm. In addition, the genome encodes both DNA and RNA polymerases.

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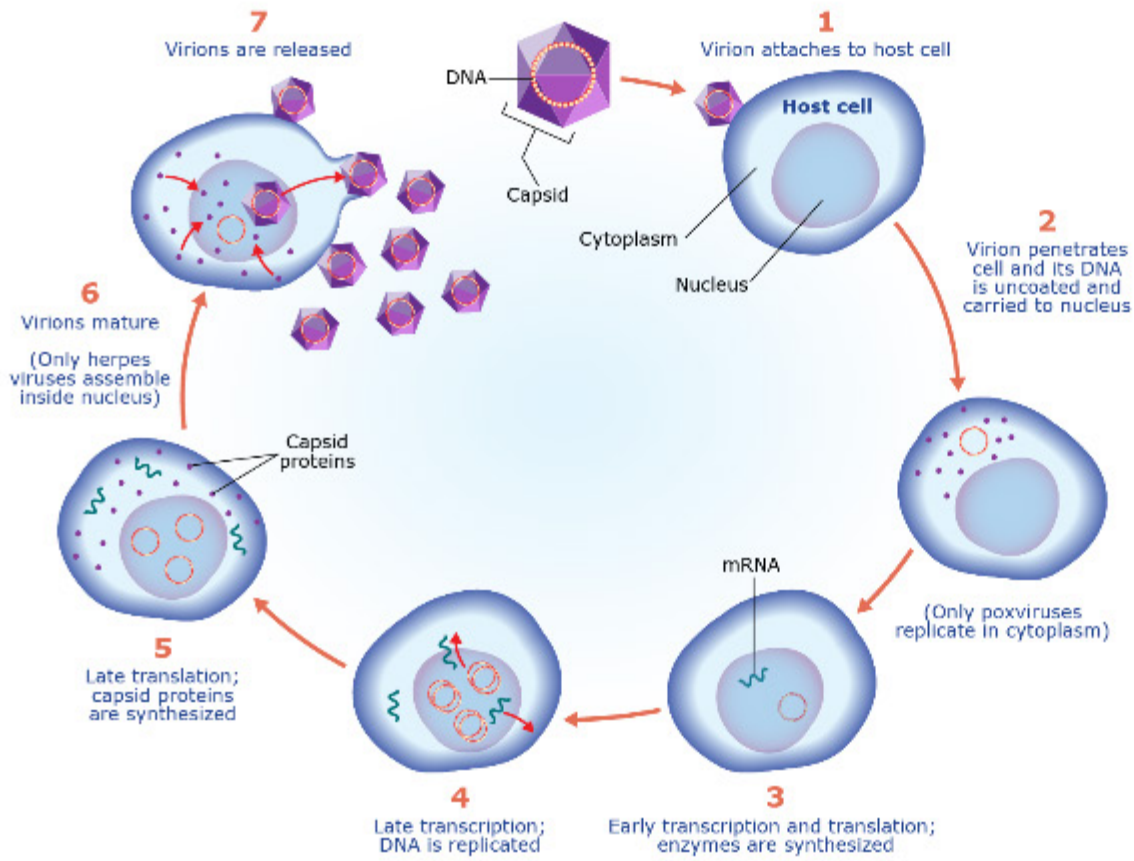
3.3 Generalized DNA Virus Life Cycle



▲ **Figure 4-3.3** Life Cycle of DNA Virus

3.4 Naked DNA Viruses

3.4.1 Parvoviridae

B19

Characteristics ssDNA, naked icosahedral

Transmission

- Respiratory route
- Blood products
- Vertical transmission

Pathogenesis

- Virus attaches to erythrocyte P antigen
- Infects and lyses erythroid progenitor cells

Clinical Syndrome Fifth disease, erythema infectiosum, slapped cheek disease

- Flu-like prodrome
- Raised, indurated facial rash
- Lacy reticular rash on remainder of body
- Aplastic crises in thalassemia and sickle cell anemia
- Adults: Rash with arthralgias due to immune complex deposition skin and joints
- Transplacental transmission: Hydrops fetalis, abortion, anemia

Diagnosis Serology, PCR

Treatment Supportive

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3.4.2 Papillomaviridae

Human Papillomavirus

Characteristics

- dsDNA, circular
- Naked, icosahedral

Transmission Direct contact/skin and fomites

Pathogenesis

- Infects basal layer of skin and mucous membranes
- Hyperkeratosis leads to warts
- Viral oncoproteins E6 and E7 cause cell cycle dysregulation and neoplastic transformation
  - E6 binds and promotes degradation of p53 (tumor suppressor)
  - E7 binds and antagonizes p105RB (retinoblastoma)
  - Causes koilocytosis, benign condylomas, or carcinoma

Clinical Syndromes

- Plantar warts: Serotype 1
- Common warts: Serotypes 2 and 4
- Anogenital warts (condyloma acuminata), laryngeal papillomas: Serotypes 6 and 11 (benign)
- Cervical intraepithelial neoplasia, penile cancer: Serotypes 16, 18, 31, 35 (preneoplastic)

Diagnosis

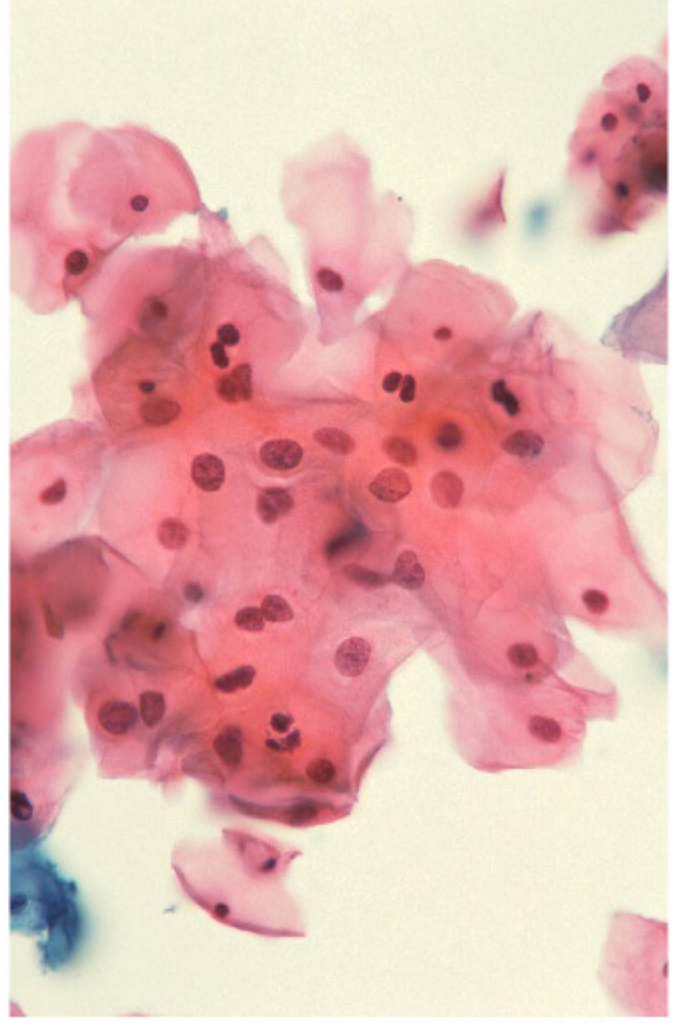
- Cutaneous warts: Clinical grounds
- Anogenital: Koilocytotic cells on Pap smear (perinuclear vacuolization and nuclear enlargement)
- DNA probes and PCR

Treatment

- Cytotoxic: Podophyllin, podophyllotoxin, 5-fluorouracil, and trichloroacetic acid
- Laser or liquid nitrogen
- Cervical lesions: Electrocautery
- Carcinoma: Radiation therapy or surgery

Prevention

- Safe sex (not a perfect solution, virus may be transmitted by skin flakes)
- Vaccine: Made by recombinant DNA, L1 capsid proteins from serotypes 6, 11, 16, and 18



DACHEZ/PHANIE/age fotostock

▲ **Figure 4-3.4** Koilocytotic Atypia on a Pap Smear

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3.4.3 Polyomaviridae

BK Virus

Transmission Respiratory or oral (early in childhood)

Clinical Syndromes Hemorrhagic cystitis and tubulointerstitial nephritis in immunocompromised patients

Diagnosis

- Virus culture
- Urine cytology—decoy cells (virus infected urothelial cells with intranuclear inclusions)
- PCR
- Kidney biopsy

JC Virus

Transmission Respiratory or oral (?)

Pathogenesis

- Targets oligodendroglial cells in the brain (also spread widely in lymphocytes)
- Giant astrocytes with intranuclear inclusions
- Foci of demyelination

Clinical Syndrome

- Progressive multifocal leukoencephalopathy in AIDS
- Hemiparesis, hemianopsia, cognitive deterioration

Diagnosis PCR of brain or CSF

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3.4.4 Adenovirus

Characteristics dsDNA, naked, icosahedral

Transmission Respiratory droplets or fecal-oral

Pathogenesis

- Epithelial cell necrosis and mononuclear infiltration
- Penton fibers act as hemagglutinins and are cytotoxic
- E3 protein inhibits MHC class 1 expression
- E1A protein makes cells susceptible to TNF and other cytokines

Clinical Syndromes

- Upper respiratory disease in children—most common serotypes 3 and 7
- Acute respiratory disease—most commonly serotypes 3, 7, 14
- Keratoconjunctivitis—serotypes 3, 19
- Acute hemorrhagic cystitis—serotype 11
- Conjunctivitis—serotype 19
- Infantile watery diarrhea or intussusception—serotypes 40 and 41

Diagnosis Serology

Treatment Supportive

Prophylaxis Live, non-attenuated vaccine delivered by enteric capsule, in military use only

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3.5 Enveloped DNA Viruses

3.5.1 Hepadnavirus: Hepatitis B (discussed previously)

3.5.2 Herpesviruses

Characteristics

- dsDNA, icosahedral
- Envelope captured from nuclear membrane, trans-Golgi network, or plasma membrane
- Lifelong latencies

Herpes Simplex Viruses

Transmission Close personal contact

Pathogenesis

- HSV-1 and -2 infect and replicate in mucoepithelial cells and produce lytic, productive infection
  - HSV-1 is most common above the waist
  - HSV-2 is most common below the waist
- Latency is established in sensory ganglia
  - HSV-1 in trigeminal, superior cervical, and vagal nerve ganglia
  - HSV-2 is most common in sacral (S2–S3) ganglia
- Stress causes recurrence
- Syncytia formation protects from immunoglobulins

Clinical Syndromes

- **Gingivostomatitis:** Painful, recurring blister-like skin vesicles
- **Eczema Herpeticum:** Children with eczema or atopic dermatitis
- **Keratoconjunctivitis:** Dendritic ulcers may lead to blindness
- **Meningoencephalitis:** Focal temporal lesions; 70% mortality if untreated
- **Genital Lesions:** Painful vesicular lesions, potential for transmission during parturition
- **Neonatal Herpes:** Disseminated; encephalitis, skin lesions, high mortality

CDC/Dr. Hermann

▲ **Figure 4-3.5A** HSV-1 Gingivostomatitis

CDC/Donated by Brian Hill of New Zealand

▶ **Figure 4-3.5B** HSV-2 Genital Lesions

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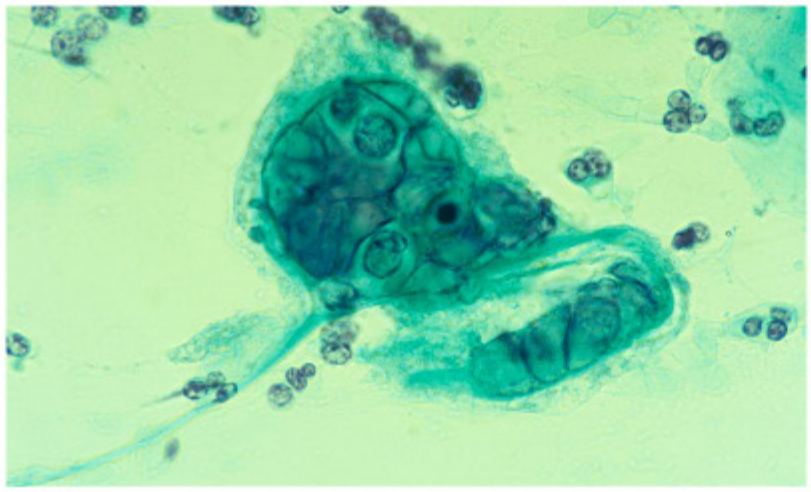
Diagnosis

- Oral or genital lesions: Clinical, Tzank smear to find syncytia at the base of vesicular lesions, Cowdry type A inclusions
- Encephalitis: PCR on CSF, one-sided temporal lesions, RBC in CSF, high opening pressure
- Virus culture



Dr. G.W. Willis/Visuals Unlimited, Inc.

▲ **Figure 4-3.5C** Tzank Smear

Treatment Acyclovir, valacyclovir, and famciclovir

- Acyclovir is a nucleoside analog, which is administered in the prodrug form
- It requires the herpes thymidine kinase to phosphorylate it
- The ring structure of the nucleoside is replaced by an open-chain structure with no 3' end
- The acyclovir monophosphate is phosphorylated by cellular kinases and becomes a potent inhibitor of the viral DNA polymerase

Varicella-Zoster Virus

Transmission Respiratory or contact with lesions

Pathogenesis

- Infection of upper respiratory tract leads to replication in regional lymph nodes
- Primary viremia causes spread into the reticuloendothelial system
- Secondary viremia associated with T lymphocytes causes infection of skin
- Latency in dorsal root ganglia
- Reactivation due to stress

Clinical Syndromes

- **Varicella (chickenpox)**
  - Fever, malaise, and headache
  - Asynchronous rash starts on the face and trunk and spreads to the entire body (red base with fluid-filled vesicle on top)
  - Pruritic

Natrow Images/Alamy

▲ **Figure 4-3.5D** Chickenpox Rash

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- **Zoster/Shingles**
  - Reactivation of latent infection from dorsal root ganglia
  - Fifth or sixth decades of life
  - Rash with burning and paresthesia along a single dermatome

Diagnosis Clinical, PCR, Tzanck smear

Treatment
- Acyclovir, valaciclovir, and famciclovir in immunocompromised patients
- Immunoglobulin available for postexposure prophylaxis of immunocompromised patients
- Aspirin contraindicated: Reye syndrome

Biophoto Associates/Science Source

▲ **Figure 4-3.5E** Zoster/Shingles Rash

Epstein-Barr Virus

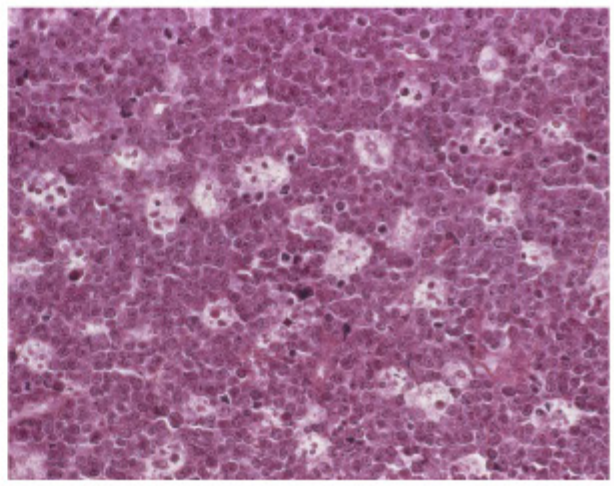
Transmission Saliva (95% of world's adult population is seropositive)

Pathogenesis
- Virus infects B lymphocytes and nasopharyngeal epithelial cells
- Infects cells that express CD21 (also known as CR2, complement C3d receptor, part of signal transduction complex)
- Produces active and non-productive infections in B lymphocytes that are polyclonally activated to produce immunoglobulin (heterophile antibodies)
- Splenomegaly and lymphadenopathy result from B cell proliferation
- Lymphocytosis up to 70% with Tc lymphocytes that recognize B lymphocyte-determined membrane antigen

Clinical Syndromes
- Heterophile-positive infectious mononucleosis:
  - Malaise, lymphadenopathy, painful exudative pharyngitis, hepatosplenomegaly, fever with or without rash
  - Complication—splenic rupture
- Hairy oral leukoplakia: Hyperproliferation of lingual epithelia in AIDS
- Lymphoproliferative disease: Persistent fever, lymphadenopathy, and hepatosplenomegaly in patients with primary or secondary immunodeficiency
- Malignancies:
  - Burkitt lymphoma
    - —Chromosomal translocation t8,14; this moves the c-myc oncogene from chromosome 8 next to the active promoter region for immunoglobulin synthesis on chromosome 14
    - —Africa and Asia
    - —Malaria may be a cofactor

CNRI/Science Source

▲ **Figure 4-3.5F** Hairy Oral Leukoplakia


Medical-on-Line/Alamy

▲ **Figure 4-3.5G** Burkitt Lymphoma

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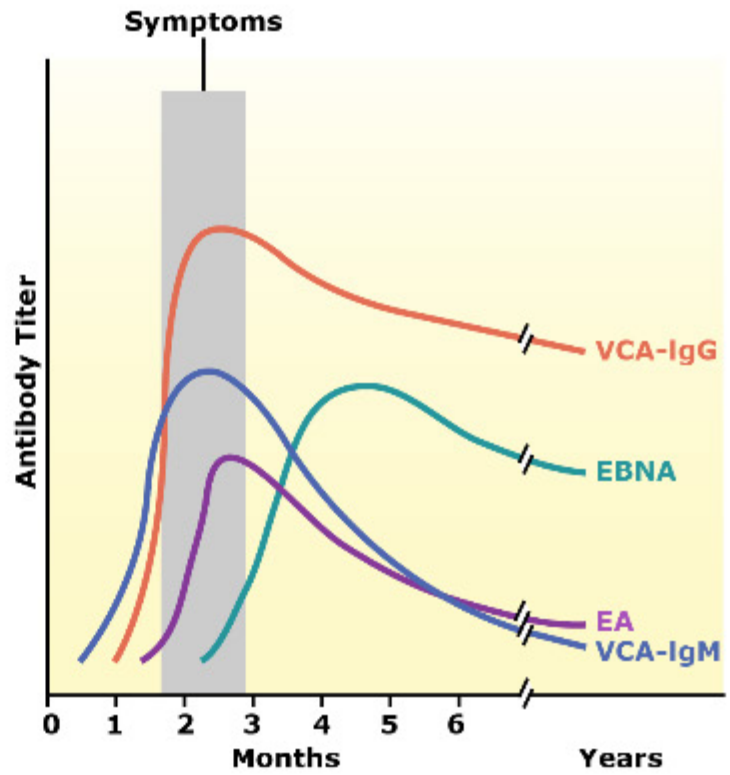
- Nasopharyngeal carcinoma: Asia, tumor cells of epithelial origin
- Hodgkin lymphoma
- Post-transplant lymphoma

Diagnosis

- Complete blood count: Up to 70% lymphocytosis, atypical reactive T lymphocytes (Downey cells)
- Monospot test: Heterophile antibodies, Paul-Bunnell antibodies (IgM antibodies that agglutinate sheep RBCs)
- Specific serologic tests:
  - 5% to 15% of adults and a greater proportion of young children and infants fail to make heterophile antibodies
  - High titer to VCA (IgM) and no titer to EBNA—acute infection
  - High titer to VCA (IgG) and EBNA—previous infection
  - Anti-EA (early antigen) antibody rises early (after VCA) and disappears in few months



▲ **Figure 4-3.5H** Serologic Test Results for Epstein-Barr Virus

Treatment

- Supportive care
- Acyclovir for hairy oral leukoplakia

Cytomegalovirus

Transmission

- Sexual, parenteral
- Transplacental
- Organ transplant, blood products

Pathogenesis

- Infects vascular endothelial cells, lymphocytes, and monocytes
- Latency in monocytes
- Immunologic damage is hypothesized to be responsible for severity of disease

Clinical Syndromes

- The No. 1 in utero infection in the United States
  - 1% of infants excrete CMV in urine or nasopharynx
  - 90% appear normal or asymptomatic, but may progress to develop sensory nerve hearing loss or psychomotor mental retardation
- Microcephaly, sensorineural deafness, thrombocytopenic purpura (blueberry muffin baby), periventricular brain calcification, and hepatosplenomegaly
- Immunocompetent adults: Heterophile-negative mononucleosis; 80% of adults are seropositive
- Immunosuppressed individuals: Retinitis (especially in AIDS), interstitial pneumonia, colitis (especially in transplant patients), esophagitis, and encephalitis

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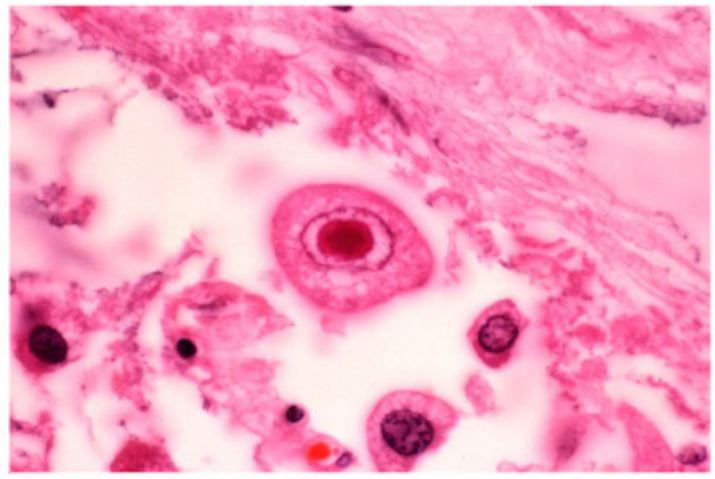
Diagnosis

- Cytopathology: Owl's eye inclusion bodies in biopsy and urine
- Culture of blood, urine, PCR
- IgM specific for CMV

Treatment Ganciclovir, foscarnet, cidofovir

Prophylaxis Blood- and organ-donor screening



Dr. Gladden Willis/Visuals Unlimited, Inc.

▲ **Figure 4-3.5I** Owl's Eye Inclusion Body

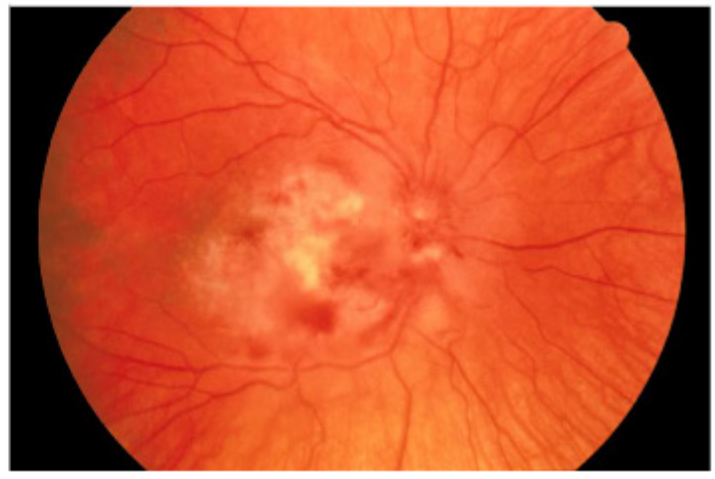
HHV-6

Pathogenesis

- T cell lymphotropic virus
- Infects children 6 months to 3 years of age

Clinical Syndromes

- Roseola infantum, exanthem subitum, sixth disease
- Abrupt onset of high fever
- Erythematous maculopapular rash, begins on the face and trunk after fever breaks
- Reactivational disease in transplant recipients—pneumonia, meningoencephalitis, bone marrow suppression



Kallista Images/Visuals Unlimited, Inc.

▲ **Figure 4-3.5J** CMV Retinitis

Diagnosis Serology or PCR

Treatment Susceptible to ganciclovir or foscarnet (not effectively susceptible to acyclovir, high doses needed)

HHV-7

Pathogenesis

- T cell lymphotropic virus
- Binds to CD4 receptor
- Infects children outside of infancy; 90% seropositive by 3 years of age

Clinical Syndromes Exanthem subitum, sixth disease

Diagnosis Serology or PCR

HHV-8 (Kaposi Sarcoma-Associated Herpesvirus, or KSHV)

Pathogenesis

- Sexual and nonsexual transmission early in childhood
- B cell lymphotropic virus
- Turns on vascular endothelial growth factor (VEGF)

Clinical Syndromes Endothelial sarcoma associated with AIDS (AIDS indicator disease)

Diagnosis Serology or PCR

Treatment IFN-α

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▼ **Table 4–3.5** Summary of Herpesvirus Infections

Name	Transmission	Clinical	Site of Latency	Diagnosis	Treatment and Prevention
Herpes simplex virus-1 (HSV-1)	Direct contact	• Mostly above the waist; below the waist on the rise • Gingivostomatitis • Keratoconjunctivitis • Encephalitis (No. 1 cause of viral encephalitis in the U.S.)—focal temporal lesions, RBC in CSF, high opening pressure	Trigeminal ganglia	• Tzanck test: Reveals multinucleated giant cells and intranuclear inclusion bodies • Viral culture • Polymerase chain reaction	• Acyclovir • Valacyclovir • Famciclovir • Condom use
Herpes simplex virus-2 (HSV-2)	Direct contact; sexual transmission	• Mostly below the waist • Genital herpes • Neonatal herpes	Sacral ganglia	• Tzanck test • Viral culture • Polymerase chain reaction	• Acyclovir • Valacyclovir • Famciclovir • Condom use
Varicella-Zoster virus	Respiratory droplets, contact with ruptured vesicles	• Varicella (chickenpox)—asynchronous vesicular rash • Zoster (shingles)—a painful eruption of vesicles isolated to a single dermatome	Dorsal root ganglia	• Tzanck test • Vesicles are described as dew drops on the top of a rose petal: A red base with fluid-filled vesicle on top, asynchronous rash	• Acyclovir • Valacyclovir • Famciclovir • Live, attenuated chickenpox vaccine • Shingles vaccine • Zoster immune globulin
Epstein-Barr virus (EBV)	Intimate contact, saliva	• Infectious heterophile-positive mononucleosis • Burkitt lymphoma • Nasopharyngeal carcinoma • Hodgkin lymphoma	B lymphocytes	• Elevated heterophile antibodies • "Atypical lymphocytes" • Serology: IgM against viral capsid antigens (VCA)	Supportive
Cytomegalovirus	Virus present in milk, saliva, urine, and tears; sexual transmission	• Asymptomatic infection • CMV mononucleosis • Reactivation in immunocompromised patients • No. 1 in utero infection in U.S.—cytomegalic inclusion disease, "blueberry muffin baby"	Mononuclear cells	• Serology • Owl's eye intranuclear inclusion bodies • PCR	• Gancyclovir • Foscarnet • Cidofovir
Human Herpesvirus 6 (HHV-6)	Close personal contact; infants to 3 years old	• HHV-6A: AIDS-associated opportunistic infection, post-transplant disease • HHV-6B: Febrile illness, roseola, post-transplant disease	T lymphocytes	Serology	Ganciclovir, foscarnet (virus has no thymidine kinase, but a different kinase product of UL97)
HHV-7	Close personal contact; children up to 3 years old	• Roseola infantum (exanthem subitum) • Binds to CD4+ T cells	T lymphocytes	Serology	None
HHV-8 (KSHV)	Sexual and nonsexual transmission	Cofactor in formation of Kaposi sarcoma, turns on VEGF	B lymphocytes	Serology	IFN-α

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3.5.3 Poxviruses

Characteristics

- Large, dsDNA, enveloped
- Complex, brick-shaped
- Synthesizes its own envelope
- Replicates in the cytoplasm
- Carries DNA-dependent RNA polymerase into the cell

Science Source

▲ **Figure 4-3.5K** Smallpox Rash

Smallpox Virus

Transmission Respiratory droplets

Pathogenesis

- Virus enters upper respiratory tract and disseminates via lymphatics
- Viremia leads to infection of dermal tissues and internal organs
- Hemorrhage into the dermis causes "pocks"

Clinical Syndrome Smallpox

- Last natural case occurred in Somalia in 1977; feared as a potential biowarfare agent
- 7- to 17-day incubation
- Flu-like prodrome
- Synchronous rash begins in mouth and spreads over entire body

Diagnosis

- Clinical
- Guarnieri bodies (cytoplasmic inclusions) found in infected cells
- Culture, PCR

Prophylaxis Live, attenuated vaccinia (cowpox) virus

Molluscum Contagiosum Virus

Transmission Direct contact, sexual, fomites, swimming pools

Pathogenesis

- Virus enters through small breaks in skin, localized infection
- Hyperplasia, ballooning degeneration, and acanthosis of epidermis
- Painless, wart-like umbilicated lesions with central caseation/indentation

Clinical Syndrome

- Children in general, young athletes or AIDS patients
- Small, pink, benign wart-like tumors or umbilicated flesh-colored papules

Diagnosis

- Clinical
- Molluscum bodies (large, eosinophilic cytoplasmic inclusions found in superficial epithelial cells)

Treatment

- Curettage
- Self-limiting in immunocompetent hosts
- Ritonavir, cidofovir in immunocompromised patients

Dr. P. Marazzi/Science Source

▲ **Figure 4-3.5L** Molluscum Contagiosum

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4 Positive-Sense RNA Viruses

4.1 Summary Characteristics for All RNA Viruses

- All are ss, except reovirus.
- All negative-sense genomes must be accompanied by polymerase.
- Reovirus and retroviruses also carry polymerases in their capsids.
- The naked RNA viruses are calicivirus, hepevirus, picornavirus, and reovirus.
- The segmented viruses are arenavirus, bunyavirus, orthomyxovirus, and reovirus.

4.2 Important RNA Viruses

▼ **Table 4–4.2** Positive-Sense RNA Viruses

Virus Family	RNA Structure	Virion Carried Polymerase	Envelope	Shape	Multiplies in	Major Viruses
Picornavirus	ss(+)RNA Linear Nonsegmented	No	Naked	Icosahedral	Cytoplasm	• Coxsackie • Echovirus • Enterovirus • Hepatitis A • Poliovirus • Rhinovirus
Calicivirus	ss(+)RNA Linear Nonsegmented	No	Naked	Icosahedral	Cytoplasm	• Noro-like virus • Norwalk agent
Hepevirus	ss(+)RNA Linear Nonsegmented	No	Naked	Icosahedral	Cytoplasm	Hepatitis E virus
Flavivirus	ss(+)RNA Linear Nonsegmented	No	Enveloped	Icosahedral	Cytoplasm	• Dengue • Hepatitis C • St. Louis encephalitis • West Nile virus • Yellow fever virus
Togavirus	ss(+)RNA Linear Nonsegmented	No	Enveloped	Icosahedral	Cytoplasm	• Rubella • EEE • VEE • WEE
Coronavirus	ss(+)RNA Linear Nonsegmented	No	Enveloped	Helical	Cytoplasm	• Coronavirus • SARS-CoV
Retrovirus	Diploid ss(+)RNA Linear Nonsegmented	RNA-dep. DNA polymerase	Enveloped	Icosahedral or truncated conical	Nucleus	• HIV • HTLV Sarcoma

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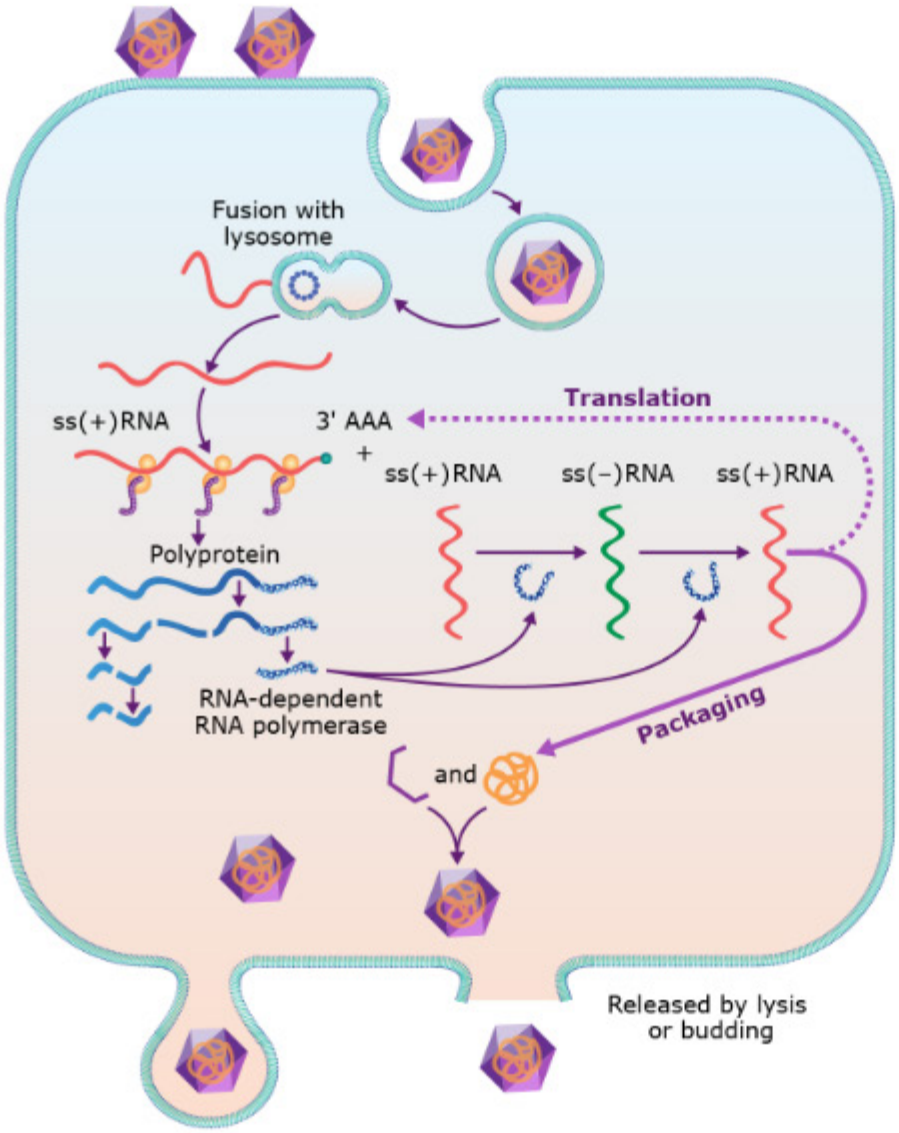
4.3 Life Cycle of the Positive-Sense RNA Viruses



▲ **Figure 4-4.3** Life Cycle of ss(+)RNA Viruses

4.4 Naked ss(+)RNA Viruses

4.4.1 Picornavirus

Characteristics

- Small, naked, icosahedral
- ss(+)RNA
- Summer/fall peak incidence

Enterovirus Genus

- Fecal-oral transmission
- Stable in acid
- Replicate best at 37ºC
- *Leading cause of aseptic meningitis*
- Infection begins in oropharyngeal mucosal cells and lymphoid tissue
- Virus moves into intestinal mucosa and gut lymphoid tissue
- Viremia causes dissemination throughout the body
- Diagnosis by serology or virus culture
- Treatment supportive and symptomatic

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Coxsackie Viruses

- **Coxsackie A**
  - A16—hand-foot-and-mouth disease
  - Herpangina
  - Aseptic meningitis
  - Acute lymphoglandular pharyngitis
  - Common cold
- **Coxsackie B**
  - Pleurodynia (Bornholm disease, devil's grip)
  - Myocarditis (No. 1 viral cause necessitating cardiac transplant)
  - Aseptic meningitis
  - Mild respiratory disease
  - Severe systemic disease of newborns
  - Possible association with type 1 diabetes

BSIP SA/Alamy

▲ **Figure 4-4.4A** Skin Rash of Hand-Foot-and-Mouth Disease

Echoviruses

- Aseptic meningitis
- Poliomyelitis-like muscle weakness
- Exanthems
- Conjunctivitis

Poliovirus

- Asymptomatic, fever of unknown origin
- Flaccid asymmetric paralysis
- No sensory loss
- Damage to anterior horn motor neurons
- Post-polio syndrome any time later, progressive muscle atrophy
- Salk (killed, injectable) vaccine used in U.S.
- Sabin (live attenuated, oral) vaccine used elsewhere

Dr. P. Marazzi/Science Source

▲ **Figure 4-4.4B** Oral Exanthem of Hand-Foot-and-Mouth Disease

Rhinovirus Genus

Characteristics

- Acid-labile
- Grows best at 33ºC
- More than 100 serotypes
- Most common cause of common cold
- Virus receptor is ICAM-1
- Peak incidence summer and fall

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Heparnavirus Genus: Hepatitis A (discussed previously)

4.4.2 Calicivirus

Characteristics

- ss(+)RNA
- Naked, icosahedral

Norwalk Virus

- School-aged child to adult
- Nausea, vomiting, watery diarrhea
- Most common cause of noninflammatory gastroenteritis in U.S.
- Diagnosis clinical or serology
- Self-limiting

Noro-Like Virus Outbreaks of viral gastroenteritis on cruise ships

4.4.3 Hepevirus: Hepatitis E (discussed previously)

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4.5 Enveloped ss(+)RNA Viruses

4.5.1 Flaviviruses

Characteristics

- ss(+)RNA
- Enveloped, icosahedral
- Arthropod-borne

Dengue Fever Virus

- Tropical geography
- *Aedes* mosquito
- Acute onset of high fever, headache, myalgias
- Hemorrhagic fever
- Break-bone fever

Hepatitis C (discussed previously)

St. Louis Encephalitis Virus

- No. 1 epidemic flaviviral encephalitis
- North American geography, lower 48 states
- *Culex* mosquito
- Febrile headache to meningoencephalitis

West Nile Virus

- Africa, Europe, Asia, North America
- Kills wild birds
- Febrile headache or encephalitis

Yellow Fever Virus

- Tropical geography
- *Aedes* mosquito
- Hemorrhage and degeneration of liver, kidney, and heart
- Live, attenuated vaccine for travelers to endemic area

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4.5.2 Togaviruses

Characteristics

- ss(+)RNA
- Enveloped, icosahedral

Rubella Virus

Transmission Respiratory droplets, transplacental

Pathogenesis

- Virus infects upper respiratory tract, replicates locally
- Spreads to other tissues via the blood

Courtesy of the Centers for Disease Control
PR. PH. Franceschini/CNRI/Science Source

▲ **Figure 4-4.5A & B** Rubella Rash: Day 1 (*left*) and Day 3 (*right*)

Clinical Syndromes

- Rubella, German measles, "three-day" measles
  - Low-grade fever, sore throat, posterior cervical lymphadenopathy
  - Erythematous maculopapular rash that begins on the face and spreads to the trunk
- In utero infections
  - Deafness
  - Congenital heart defects, such as PDA and VSD
  - Mental retardation, microcephaly
  - Ophthalmic problems, such as cataracts and chorioretinitis
  - Intrauterine growth retardation, thrombocytopenic purpura, and hepatosplenomegaly
  - Progressive post-rubella panencephalitis (develops in teens; death within eight years)

Diagnosis Serology and virus culture

Treatment Supportive

Prevention Live, attenuated vaccine (part of MMR)

Courtesy of the Centers for Disease Control

▲ **Figure 4-4.5C** Congenital Rubella Cataracts

Eastern, Western, and Venezuelan Equine Encephalitis Viruses

Transmission Mosquito-borne, bird reservoir

- EEE—Eastern U.S. and Canada (summer months)
- WEE—Western U.S (summer months)
- VEE—Central and South America

Clinical Syndrome

- Sudden onset fever, general myalgia, headache of increasing severity
- Seizures and coma

Diagnosis Serology, PCR

Martin M. Rotker/Science Source

▲ **Figure 4-4.5D** Congenital Rubella Microcephaly

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4.5.3 Coronavirus

Characteristics

- ss(+)RNA
- Enveloped, helical

Coronavirus

- Second most common cause of the common cold
- Winter-spring peak incidence

Severe Acute Respiratory Syndrome (SARS)

- **Transmission:** Respiratory droplets, possible airborne; last human case in 2004, but host reservoir in China/East Asia is likely among animals (possibly bats)
- **Clinical Syndrome:** High fever, flu-like, progressive hypoxia
- **Diagnosis:** Serology, RT-PCR, virus culture
- **Treatment:** Supportive, ribavirin (experimental)

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4.5.4 Retroviruses

Characteristics

- ss(+)RNA, diploid
- Enveloped, modified icosahedral
- Virion-carried RNA-dependent DNA polymerase

Oncovirus Group

Human T Cell Leukemia Virus 1 and 2

Transmission

- Sexual, parenteral
- Geography: Japan, Caribbean, and Central Africa

Pathogenesis

- The virus binds to CD4 T lymphocytes
- Viral Tax protein increases production of IL-2 and IL-2 receptors
- Product of *hbz* gene promotes clonal expansion of infected lymphocytes
- Latency up to 30 years

Clinical Syndrome Adult T cell leukemia-lymphoma (ATLL)

Diagnosis

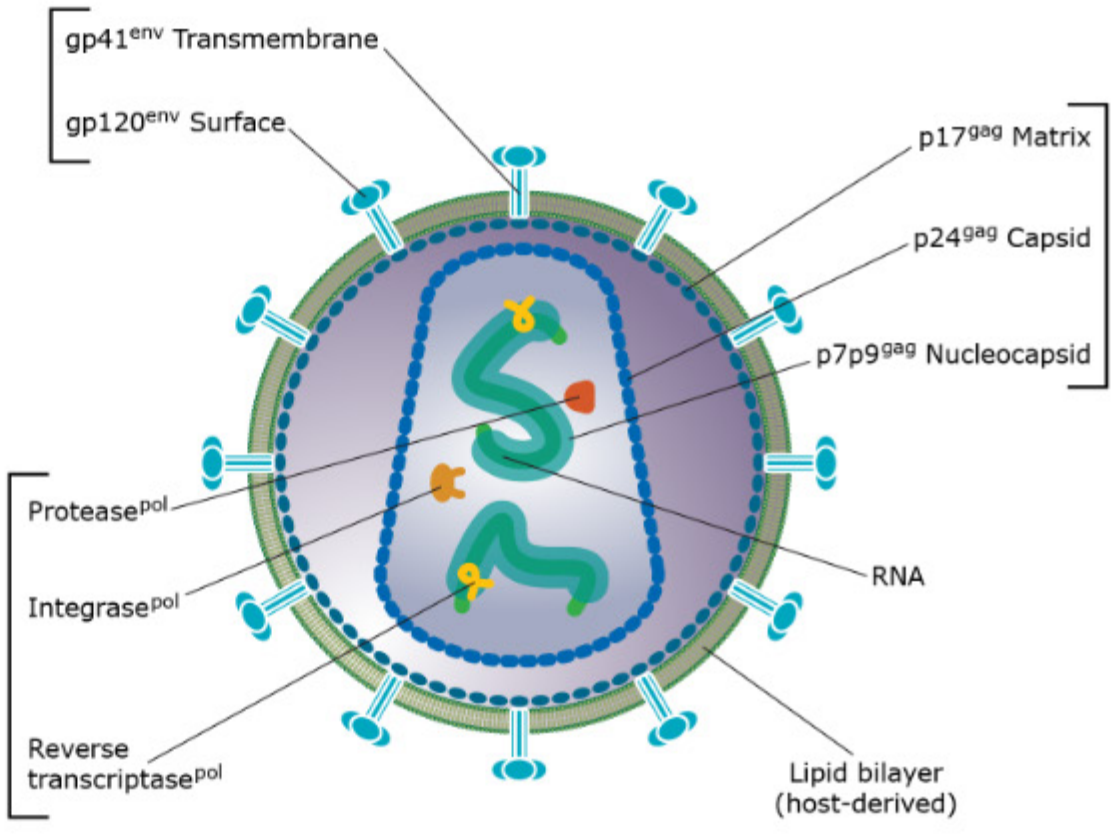
- Malignant T cells have a flower-shaped nucleus
- Sezary syndrome-like skin lesions
- RT-PCR for viral RNA, ELISA

4.5.5 Lentiviruses

Human Immunodeficiency Virus (HIV)

Characteristics

- ss(+)RNA, diploid
- Enveloped, icosahedral
- Truncated conical capsid
- Carries RNA-dependent DNA polymerase, integrase and protease enzymes
- Binds to CD4 and uses CXCR4 and CCR5 chemokine coreceptors



▲ **Figure 4-4.5E** Anatomy of HIV

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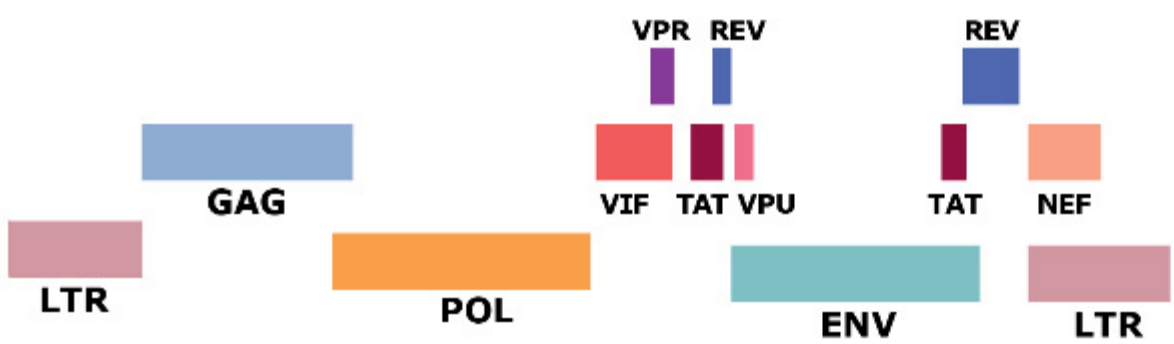

▲ **Figure 4-4.5F** HIV Genome

▼ **Table 4–4.5A** HIV Genes

Gene	Product	Function
Structural Genes		
Env (envelope)	gp120	Surface protein that determines tropism; binds CD4 and chemokine co-receptors, changes cause genetic drift
	gp41	Fusion protein, fuses viral envelope to cell, contributes to syncytia formation
Gag (group specific antigens)	p24	Capsid antigen
	p7p9	Nucleocapsid proteins
	p17	Matrix protein
Pol (polymerase)	Integrase	Integrates provirus into chromosomes; target of raltegravir
	Protease	Cleaves long peptide chains into appropriate subunits; target of "inavir" drugs
	Reverse transcriptase	Creates dsDNA provirus. Extremely error-prone. Causes genetic shift.
Regulatory and Accessory Proteins		
LTRs	Long terminal repeats in DNA (U3, U5)	"Sticky ends" recognized by integrase enzyme, provide promoter/enhancer function once integrated
tat	Tat	Transcriptional activator
rev	Rev	Promotes transport of unspliced mRNAs from nucleus to cytoplasm
nef	Nef	Down-regulation of cellular CD4 and MHC 1 expression, essential for progression to AIDS
vpu	Vpu	Facilitates virus assembly and release
vpr	Vpr	Facilitates nuclear entry in nondividing cells, arrests cell division
vif	Vif	Increases viral infectivity

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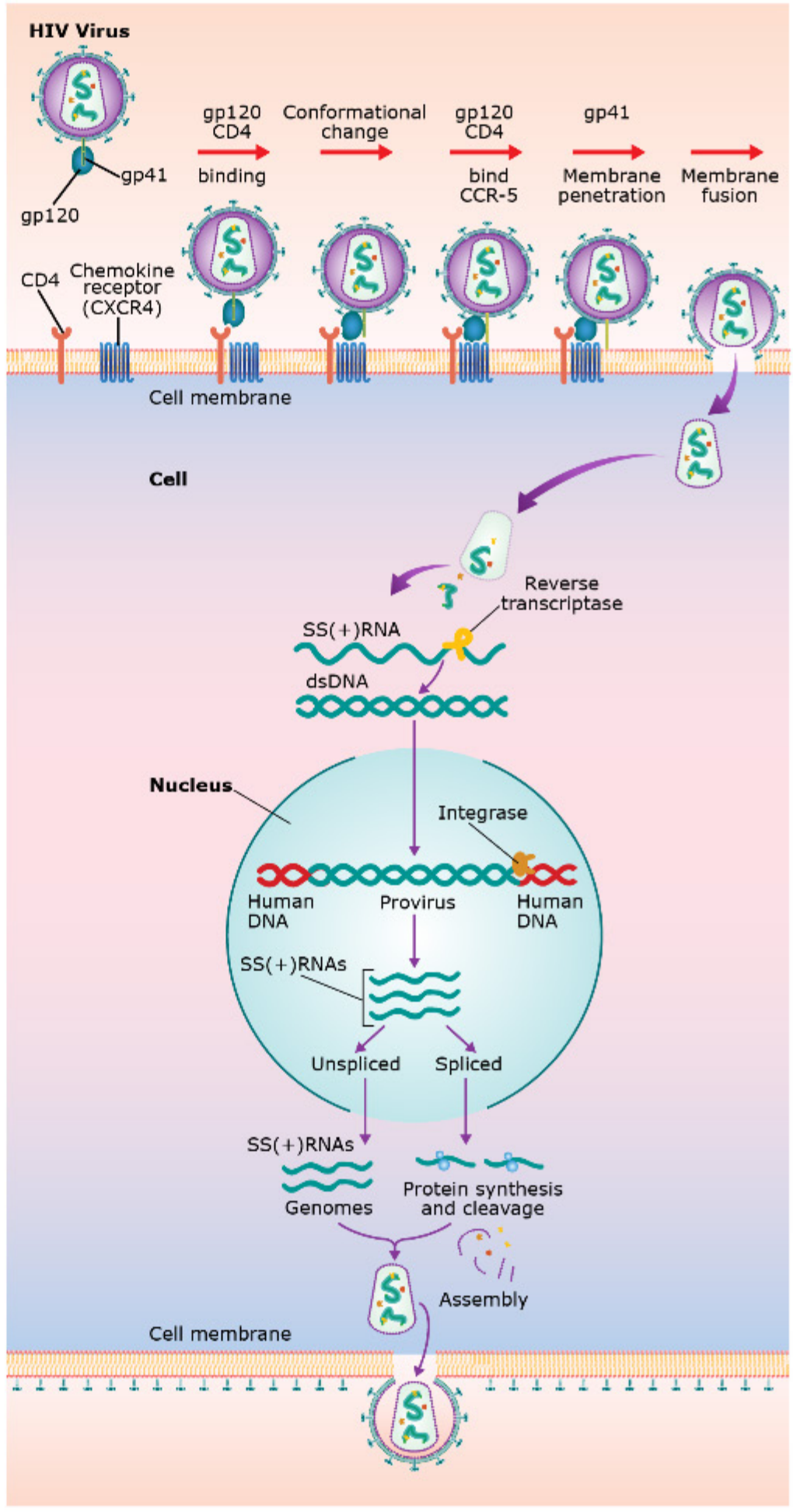
Transmission Sexual, parenteral (exchange of body fluids), transplacental, transmammary

Life Cycle

- Infection begins with the binding of HIV gp120 to CD4 and a chemokine receptor (CCR5) found on monocytes, macrophages, and dendritic cells. Later in infection, CXCR4 on the cells serves as the coreceptor.
- The virus is taken up by viropexis using the fusion protein gp41 and the nucleocapsid is released into the cytoplasm of the cell.
- The virus is taken up by viropexis using the fusion protein gp41 and the nucleocapsid is released into the cytoplasm of the cell.
- Viral reverse transcriptase makes a dsDNA copy of the genome, which migrates to the nucleus.
- The integrase enzyme integrates the viral DNA into the chromosome creating the provirus. From this point onward, any natural cloning of the infected cell will also clone proviral DNA.
- The rate of the continuation of the viral life cycle is regulated by regulatory proteins *tat*, *rev*, and *nef*.
- Transcription from the proviral DNA is performed using cellular transcriptase enzymes. Cleaved RNA is used as mRNA; uncleaved molecules will become genomic copies for the next generation.
- Translation using cellular mechanisms produces long proteins that are cleaved by the viral protease enzyme.
- Virions are assembled and the progeny are released by budding.



▶ **Figure 4-4.5G** HIV Life Cycle

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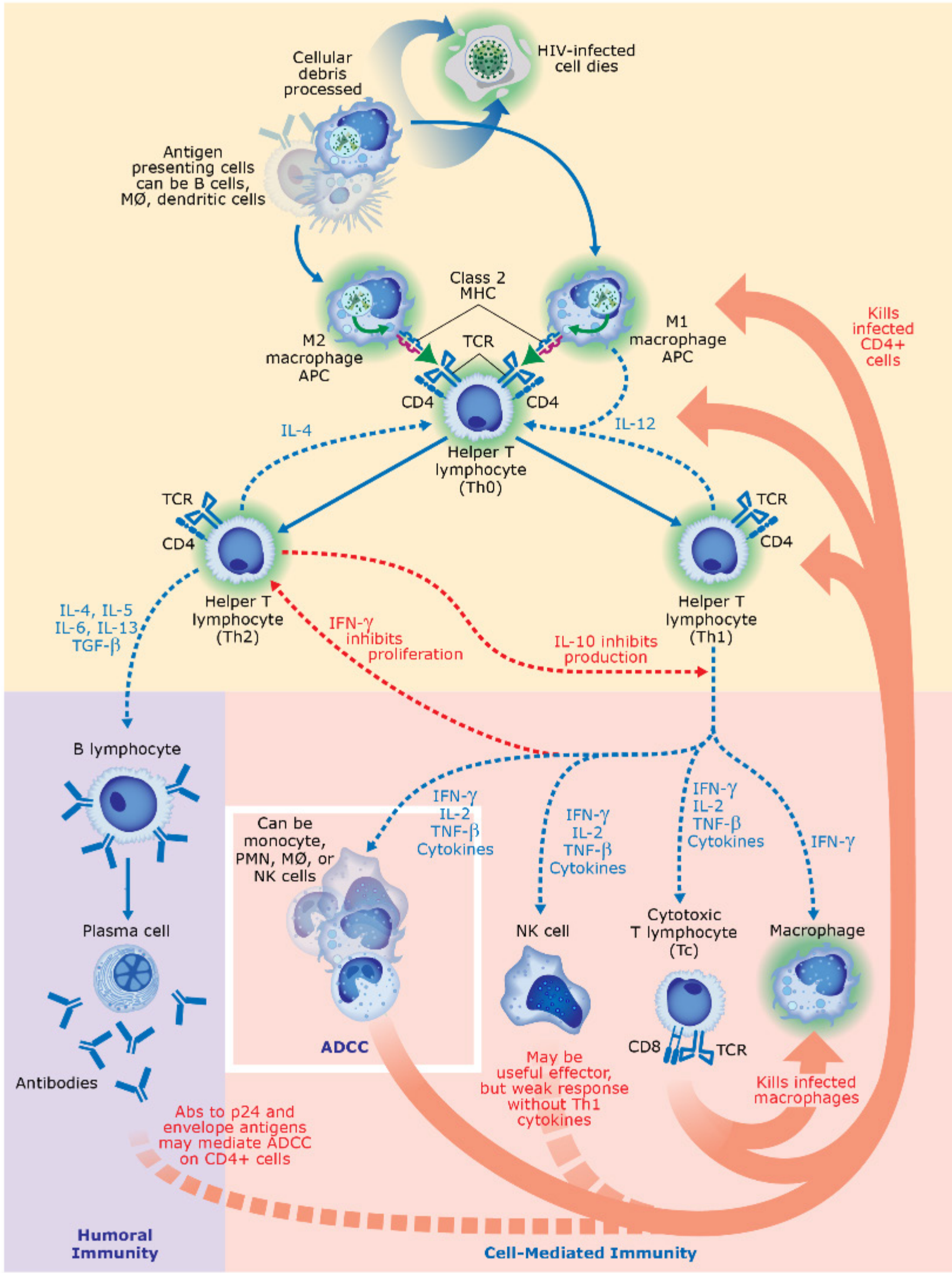

▲ **Figure 4-4.5H** The Global Effects of HIV Infection on the Immune Response

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Acute Infection

- Infection in macrophages is established. These cells resist the cytopathic effects of the virus, but serve as a reservoir of infection, and contribute to the spread of the virus throughout the body.
- A strong immune response against the virus produces antibodies, and cytotoxic T cells seem to control the virus for a time.
- This stage of disease may be asymptomatic or present with mononucleosis-like symptoms and lasts from two to six weeks.
- The normal value of CD4 T cells in the blood at this time is 800 to 1200/μL.

Clinical Latency

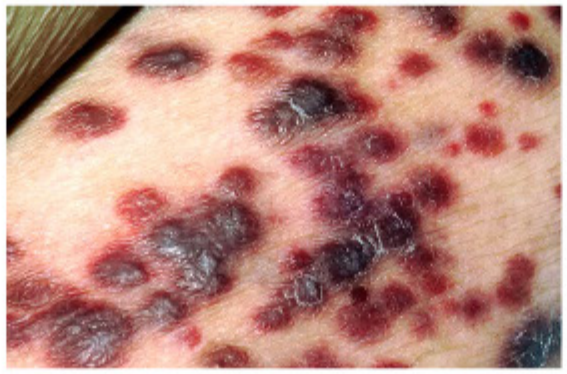
- Antibodies against viral proteins contribute to the decline of viremia, but the virus continues to replicate rapidly in infected cells.
- Latency is controlled by specific viral proteins: *tat* and *rev* genes upregulate virus production.
- The length of latency varies between patients, but generally lasts until the CD4 cell count falls below 600 CD4 cells/μL.

Early Symptomatic

- Ongoing mutation during infection allows escape from the immune response *and* leads to antiviral drug resistance.
- There is a shift in viral preference from CCR5 to CXCR4 co-receptors (found primarily on Th cells).
- CD4+ T cells are lost through viral lysis, fragility of fused Th cell syncytia, CD8+ T cell killing, complement mediated lysis, and apoptosis.
- The CD4 T cell count falls below 400/μL, IgG antibodies against p24 antigen can no longer be produced, and the viremia returns.
- Constitutional symptoms such as fever, diarrhea, fatigue, and weight loss begin.
- Mild opportunistic diseases such as bacillary angiomatosis, oral and vaginal candidiasis, listeriosis, etc., increase in incidence.

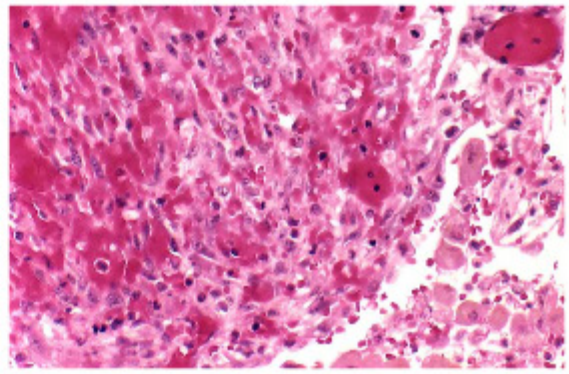
Acquired Immunodeficiency Syndrome (AIDS)

- As CD4+ T cells fall below 200 per μL, virus titer rises rapidly and the remaining immune response (including CD8+ T cells) collapses.
- Patients are now susceptible to severe opportunistic infections such as *Pneumocystis* pneumonia; candidiasis of the esophagus, bronchi, trachea, or lungs; histoplasmosis; atypical mycobacterial infection; cryptosporidiosis; and cerebral toxoplasmosis.



National Cancer Institute/Science Source

▲ **Figure 4-4.5I** Kaposi Sarcoma, Skin Lesions



CDC/Dr. Edwin P. Ewing, Jr.

▲ **Figure 4-4.5J** Kaposi Sarcoma, Microscopic

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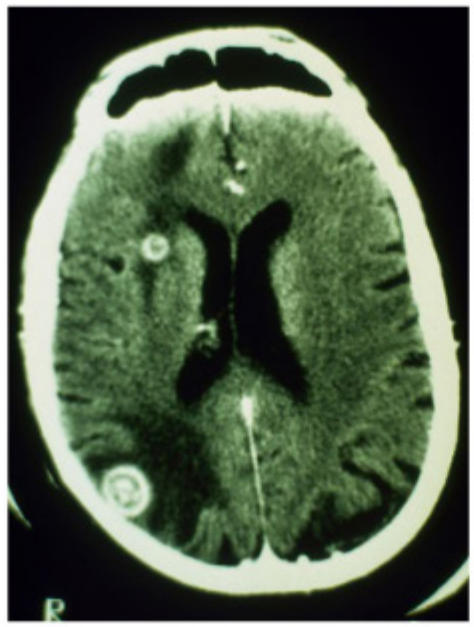
Pr. Bourrey/Science Source

▲ **Figure 4-4.5K** Toxoplasmosis Ring-Enhancing Lesions in AIDS

▼ **Table 4–4.5B** CDC Staging of HIV Infection

CD4+ T cells/µL	Category A	Category B	Category C
> 1,000	(Excludes conditions in B and C); Acute (primary) or asymptomatic HIV infection; Persistent generalized lymphadenopathy	Symptomatic but not conditions in C; Condition attributed to HIV infection or indicative of a defect in cell-mediated immunity	AIDS-defining conditions
> 500	A1	B1	C1
200–499	A2	B2	C2
< 200	A3	B3	C3

Diagnosis and Laboratory Analysis A variety of techniques are available to diagnose HIV infection and monitor patient response to therapy:

- Initial screening: EIA for anti-HIV antibodies
- Confirmation: Western blot for HIV antibodies
- Determination of viral load: RT-PCR (detects RNA in virions in the blood; viral load has been shown to be the best long-term indicator of a patient's response to therapy)
- Diagnosis of infection in a newborn: PCR (detects proviral DNA)
- Early marker of infection: p24 antigen
- Progression of disease: CD4:CD8 ratio

Antiretroviral Therapies The standard antiretroviral "cocktail" consists of two RT inhibitors (nucleoside or non-nucleoside) and one protease inhibitor.

Prophylaxis Blood and organ screening, safe sex, no vaccine yet available.

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▼Table 4–4.5C HIV Therapies

RT Inhibitors (Nucleoside Analogues)	RT Inhibitors (Non-nucleoside)	Protease Inhibitors	Fusion Inhibitors	Receptor Antagonists	Integrase Inhibitors
Abacavir (ABC)	Delavirdine	Amprenivir	Enfuvirtide (T-20) Fuzeon	Maraviroc (CCR5 antagonist)	Raltegravir
Didanosine (ddI)	Nevirapine	Indinavir			
Lamivudine (3TC)	Efavirenz	Atazanivir			
Emtricitabine (FTC)		Nelfinavir			
Stavudine (d4T)		Ritonavir			
Zalcitabine (ddC)		Saquinavir			
Tenofovir (nucleotide prophylactic)					

▼Table 4–4.5D CDC Recommendations for Standard Prophylaxis

CD4+ T cells/µL	Opportunistic Organisms	Therapy
< 200	*Pneumocystis jirovecii*	Trimethoprim sulfamethoxazole
< 100	*Histoplasma capsulatum* (in the endemic area)	Itraconazole
	Toxoplasma gondii	Trimethoprim sulfamethoxazole
< 50	Cytomegalovirus	Ganciclovir, valganciclovir
	Mycobacterium avium intracellulare	Azithromycin or clarithromycin
	Cryptococcus neoformans	Fluconazole
	Cryptosporidium parvum	Hygienic recommendations, nitazoxanide

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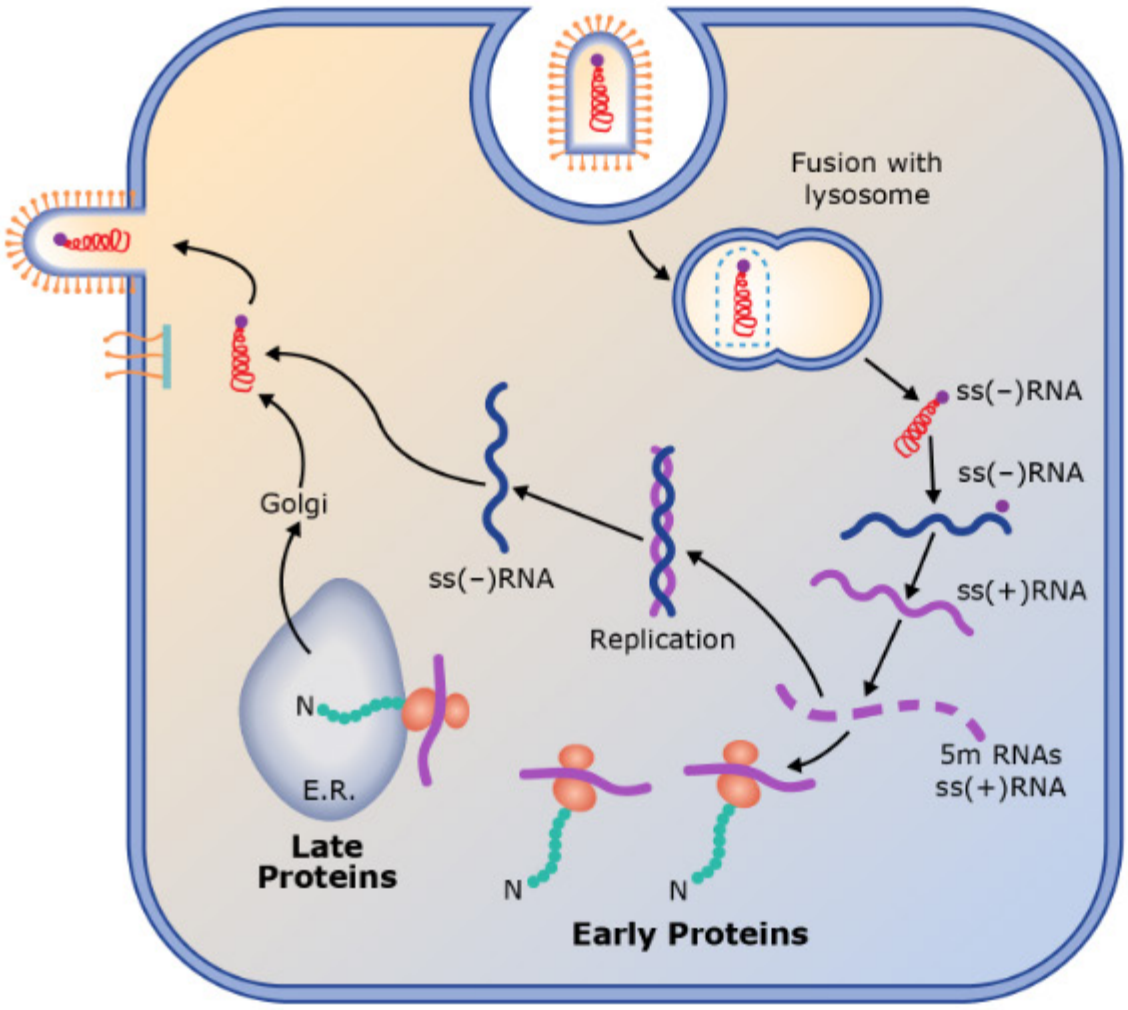
5 Negative-Sense RNA Viruses

5.1 Life Cycle



▲ **Figure 4-5.1** Life Cycle of ss(−)RNA Viruses

5.2 Molecular Characteristics

These viruses are identified by the presence of particular molecules in their anatomy:

- **Hemagglutinin:** Binds to sialic acid, mediates virus attachment to the host cell
- **Neuraminidase:** Cuts off sialic acid residues and aids release of the virus
- **Matrix Protein:** Underlies the envelope and stabilizes it
- **Fusion Protein:** Fuses viral envelope to cell, contributes to syncytia formation

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5.3 Summary of ss(–)RNA Viral Families

▼**Table 4–5.3** ss(–)RNA Viral Families

Virus	RNA Structure	Envelope	Shape	Multiplies in	Major Viruses
Rhabdovirus	ss(–)RNA Linear Nonsegmented	Yes	Bullet-shaped, helical	Cytoplasm	• Rabies • Vesicular stomatitis virus
Paramyxovirus	ss(–)RNA Linear Nonsegmented	Yes	Helical	Cytoplasm	• Mumps • Measles • Respiratory syncytial virus • Parainfluenza virus
Filovirus	ss(–)RNA Linear Nonsegmented	Yes	Helical	Cytoplasm	• Marburg • Ebola
Arenavirus	ss(–)RNA 2 segments: end-to-end circle, ambisense	Yes	Helical, ribosomes in virion	Cytoplasm	• Lymphocytic choriomeningitis virus • Lassa fever virus
Bunyavirus	ss(–)RNA Linear to circular 3-segmented	Yes	Helical	Cytoplasm	• California encephalitis • LaCrosse encephalitis • Hantavirus
Orthomyxovirus	ss(–)RNA Linear 8-segmented	Yes	Helical	Cytoplasm and nucleus	Influenza

5.4 Nonsegmented Negative-Sense RNA Viruses

5.4.1 Rhabdoviruses

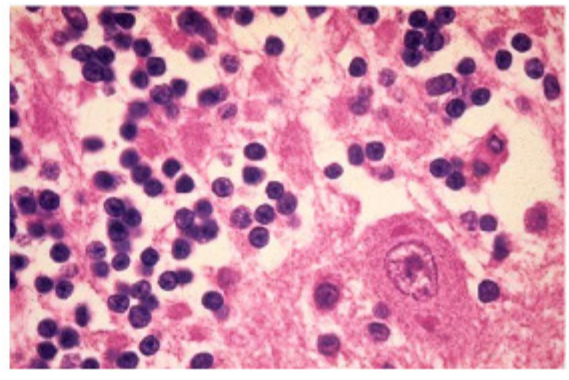
Characteristics

- Negative-sense, ssRNA
- Enveloped, helical, bullet-shaped

Rabies Virus

Transmission Bite or contact with reservoir animal

- Raccoon: East of the Mississippi River
- Skunk: West of the Mississippi River



Dr. John D. Cunningham/ Visuals Unlimited, Inc.

▲**Figure 4-5.4A** Rabies Virus

Pathogenesis

- Virus binds to nicotinic acetylcholine receptors of nerve or muscle cells at the bite site
- Virus moves by retrograde axoplasmic transport to the dorsal root ganglia and spinal cord
- Spread to the brain causes encephalitis, coma, and death

Clinical Syndrome

- Prodromal stage with pain or itching at the site of the wound
- Fever, headache
- Neurologic symptoms: Salivation, hydrophobia, seizures, hallucinations, paralysis, coma, and death

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Diagnosis

- Clinical
- Direct fluorescent antibody test of corneal epithelial cells
- PCR
- Brain biopsy: Negri bodies (eosinophilic intracytoplasmic inclusions)

Treatment If symptoms are present, none; rabies is invariably fatal

Post-exposure Prophylaxis

- Antirabies immunoglobulin into the wound
- Five doses of killed vaccine, on days 0, 3, 7, 14, and 28

5.4.2 Paramyxovirus

Characteristics

- Negative-sense, ssRNA
- Helical, enveloped, nonsegmented
- All are syncytial viruses (possess a fusion protein)

Measles Virus

Characteristics

- Single serotype
- Hemagglutinin and fusion protein, but no neuraminidase

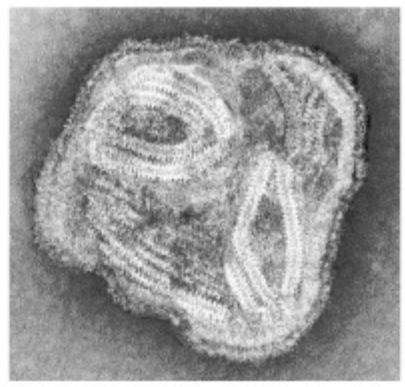
Transmission Aerosol

Pathogenesis

- The virus replicates in the respiratory tract following inhalation
- It moves into the lymphatic tissues and the blood, causing viremia
- It infects T and B lymphocytes, monocytes, and neutrophils without cytolysis, but with impairment of their immunologic function
- It inhibits IL-12 production by monocytes and macrophages, antibody synthesis in B lymphocytes, and NK function
- Syncytia formation evades antibody-mediated immunity

Clinical Syndromes

- **Measles**
  - Cough, coryza and conjunctivitis, fever, malaise, photophobia
  - Koplik spots (small red-based lesions with blue-white centers in mouth)
  - Nonpruritic, maculopapular rash begins on the face and spreads to the trunk and extremities
  - Giant cell pneumonia (Warthin-Finkeldey cells)



Dr. Linda M. Stannard, University of Cape Town/Science Source

▲ **Figure 4-5.4B** Electron Micrograph of Measles Virus

Science VU/CDC/Visuals Unlimited, Inc

▲ **Figure 4-5.4C** Koplik Spots

Lowell Georgia/Science Source

Science Source

▲ **Figure 4-5.4D** The Measles Rash

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- **Subacute Sclerosing Panencephalitis (SSPE)**
  - Fatal neurologic sequela in 1/100,000 cases of measles
  - Two to 10 years after infection
  - Buildup of defective virus particles in the brain
  - Behavioral changes, intellectual deterioration, ocular abnormalities, myoclonic jerks

Diagnosis
- Clinical
- Isolation of virus from nasopharynx or urine
- PCR

Treatment Supportive

Prevention Live, attenuated vaccine; M in MMR

Mumps Virus

Characteristics
- Single hemagglutinin-neuraminidase glycoprotein, fusion protein
- Single serotype

Transmission Respiratory droplets

Pathogenesis
- Virus replicates in the respiratory tract, lymphoid tissue, and bloodstream
- It then spreads to the salivary glands, kidney, and CNS
- Tissue response is cell necrosis and inflammation with mononuclear cell infiltration
- Desquamation of necrotic epithelial lining cells in dilated ducts

Clinical Syndromes
- Fever, anorexia, malaise, myalgia, and inflamed, tender parotid glands (parotitis)
- Secondary complications can include pancreatitis, orchitis in adult males, meningoencephalitis, and polyarthritis

Diagnosis
- Clinical, amylase may be elevated
- Virus isolation from saliva, CSF, urine
- Serology: EIA

Treatment Supportive care

Prevention Live, attenuated vaccine (MMR)

CDC/Patricia Smith/Barbara Rice

▲ **Figure 4-5.4E** Mumps-Associated Parotitis

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Parainfluenza Virus

Characteristics

- Single hemagglutinin-neuraminidase glycoprotein
- Fusion protein

Transmission Respiratory droplets

Pathogenesis

- Similar to influenza viruses
- Subglottic airway obstruction leads to inspiratory stridor, dyspnea, hoarseness, and a "seal bark" cough

Clinical Syndrome

- Croup (laryngotracheobronchitis), bronchiolitis, and pneumonia
- Children 6 months to 3 years

Diagnosis PCR or serology

Treatment Supportive

Respiratory Syncytial Virus

Characteristics

- G glycoprotein mediates attachment
- F protein produces fusion (syncytia)
- No hemagglutinin or neuraminidase molecules

Transmission Respiratory droplets

Pathogenesis

- Infection is confined to the respiratory epithelium; viremia occurs rarely
- Th2 responses may cause more severe disease
- Necrosis of epithelial cells, interstitial mononuclear infiltrates, multinucleated giant cells

Clinical Syndromes

- Bronchiolitis and pneumonia in infants 6 weeks to 6 months of age
- Cough, tachypnea, respiratory distress, hypoxemia, and cyanosis
- Adults: Common cold

Diagnosis

- Immunofluorescence, PCR
- Syncytia formation in cell culture

Treatment Supportive care

Prophylaxis Palivizumab (monoclonal against fusion protein) is given prophylactically to high-risk groups

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5.4.3 Filovirus

Characteristics

- ss(−)RNA, nonsegmented
- Enveloped, helical
- Filamentous

Transmission Reservoir in African simians and Old World rodents; direct contact, blood, secretions

Clinical Syndromes

- Marburg fever and Ebola fever
- Fatal hemorrhagic fevers
- Replicate in vascular endothelium and cause necrosis

Diagnosis EIA, PCR

Treatment Supportive, quarantine

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5.5 Segmented Negative-Sense RNA Viruses

5.5.1 Arenavirus

Characteristics

- ss(−)RNA, two segments; one negative sense, one ambisense
- Enveloped, helical
- Ribosomes carried in virion

▼ **Table 4–5.5A** Arenaviruses

Virus	Source	Presentation	Diagnosis	Treatment
Lassa fever	West Africa, contact with infected rodents, person-to-person	Fever, hemorrhagic shock, neurologic disturbances, bradycardia, hepatitis, myocarditis, deafness	Clinical, with travel history	Supportive, ribavirin
Lymphocytic choriomeningitis virus	Hamsters and mice, rodent breeding colonies or pet centers	Fever, headache, myalgia, meningitis, meningoencephalitis	History of rodent contact, serology	Supportive, ribavirin

5.5.2 Bunyavirus

Characteristics

- ss(−)RNA, three segments
- Enveloped, helical

▼ **Table 4–5.5B** Bunyaviruses

Virus	Source	Presentation	Diagnosis	Treatment
Hantavirus (Sin Nombre virus)	Inhalation from nesting rodent excretions, spring months	Four-corners states (Utah, New Mexico, Colorado, Arizona), acute pulmonary edema, effusion, 35% mortality	Serology, PCR	Respiratory support, ribavirin experimental
California and La Crosse encephalitis viruses	Chipmunks, *Aedes* mosquito	Encephalitis with seizures, 5–18 year olds, Midwest (Wisconsin, Ohio, Minnesota, Indiana, and West Virginia)	Serology	Supportive

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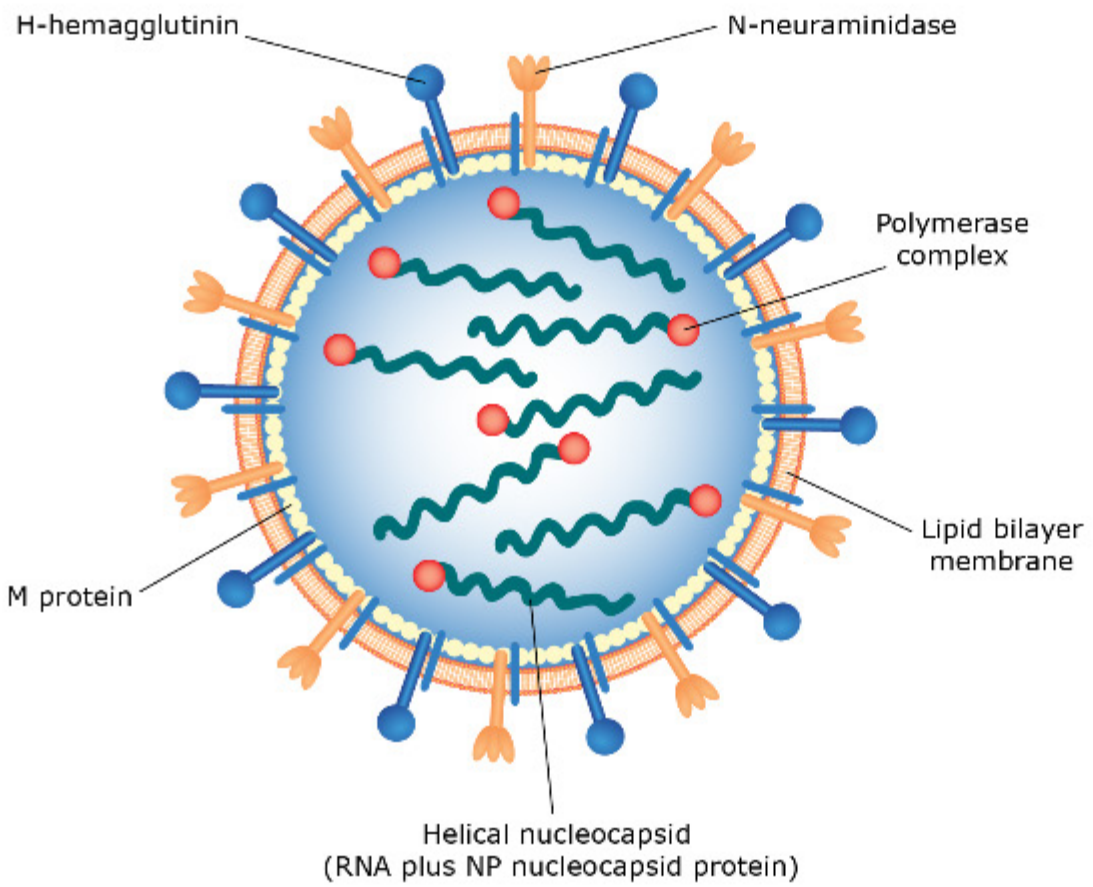
5.5.3 Orthomyxovirus

Characteristics

- ss(−)RNA, eight segments.
- Enveloped, helical.
- Requires cell nucleus to cannibalize capped 5' termini of cellular RNA for use as primers for viral mRNA transcription.
- *Genetic drift* (influenza A and B): Mutational changes in hemagglutin and/or neuraminidase molecules lead to *epidemics*.
- *Genetic shift* (influenza A): When animal and human influenza viruses co-infect a cell, accidental reassortment of the segments of the genomes can lead to the sudden appearance of progeny viruses that are drastically different from their parental strains. This can cause *pandemics* of disease because of the lack of "herd immunity" to this new variant. The 2009 H1N1 ("swine flu") virus was a quadruple reassortment virus: North American swine, avian, and human plus Asian/European swine.



▲ **Figure 4-5.5A** Anatomy of Influenza Virus

Science VU/Visuals Unlimited, Inc.

▲ **Figure 4-5.5B** Electron Micrograph of Influenza Virus

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Influenza Virus

Transmission Aerosol

- Influenza A reservoir: Humans, pigs, birds
- Influenza B reservoir: Humans only

Pathogenesis

- Hemagglutinin molecule mediates attachment to sialic acid containing glycoproteins or glycolipids on respiratory cell surfaces
- Virus multiplies in ciliated respiratory epithelial cells causing death and desquamation of both mucus-producing and ciliated cells
- Loss of the mucociliary escalator makes the patient prone to bacterial superinfection
- Neuraminidase splits off the terminal neuraminic (sialic) acids preventing possible multiple infections of one cell, and also plays an important role in viral release

Clinical Syndromes

- Influenza
  - Abrupt onset of fever, headache, myalgias
  - Dry, non-productive cough
- Complications
  - Reye syndrome
    - Rash
    - Vomiting
    - Liver damage associated with aspirin use
  - Guillain-Barré syndrome
    - Flaccid, ascending paralysis
    - Antibodies against myelin proteins
    - Causes demyelination and polyneuropathy

Diagnosis

- Clinical, season
- Serology

Treatment

- Supportive
- Amantadine/rimantidine: Prevent the uncoating of influenza A; current isolates are resistant
- Zanamivir and oseltamivir: Neuraminidase inhibitors which can be used for influenza A and B

Prophylaxis

- Killed, injectable vaccine produced yearly; epidemiologic "best guess" of two most likely A strains and one B strain; prepared in eggs
- Live, attenuated vaccine of similar composition but for intranasal administration available for use in individuals 2 to 49 years of age

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6 Double-Stranded RNA Viruses

6.1 Family Characteristics

▼ **Table 4–6.1** Characteristics of Double-Stranded RNA Viruses

Family	Structure	Virion Carried Polymerase	Envelope	Shape	Viruses
Reovirus	Linear, dsRNA, 10–11 segments	Yes	Naked	Icosahedral, double shelled	• Reovirus • Rotavirus • Colorado tick fever virus

6.2 Medically Important Reoviruses

▼ **Table 4–6.2** Reoviruses

Virus	Transmission	Syndrome	Diagnosis	Treatment	Prophylaxis
Reovirus	Fecal-oral, respiratory	Common cold, gastroenteritis	Serology	Supportive	Hygiene
Rotavirus	Fecal-oral	Infantile watery diarrhea	EIA	Supportive	Live, attenuated oral vaccine
Colorado tick fever virus	Tick-borne (*Dermacentor*)	Headache, myalgia, fever, encephalitis	Serology	Supportive	Tick avoidance

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7 Prions—Small Proteinaceous Infectious Particles

7.1 Characteristics

- Protein encoded by a normal cellular gene (PrPc) is converted into a disease-causing form (PrPsc) by change in conformation.
- Particles are not inactivated by formalin, ionizing radiation, boiling, or most disinfectants.
- No nucleic acids or other virion structures.
- Do not elicit an inflammatory response.
- Cause invariably fatal subacute spongiform encephalopathies (amyloidopathies of the brain).

7.2 Examples of Prion Diseases in Humans

▼ **Table 4–7.1** Prion Diseases in Humans

Disease	Source	Age of Onset	Mean Time to Death
Kuru	Cannibalism of brain tissue	4–20 years after ingestion	6 months after symptom onset
Creutzfeldt-Jakob disease	Sporadic, familial, or corneal transplant and dura mater grafts	6th–7th decades of life	4–7 months
Variant Creutzfeldt-Jakob disease	Ingestion of infected bovine neural tissue or bone marrow	Variable after ingestion	14 months
Gerstmann-Sträussler-Scheinker syndrome	Familial, sporadic	4th–5th decades of life	5 years
Fatal familial insomnia	Familial	35–61 years of age	13–25 months

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Chapters 3–4 Review Questions

1. A bacterial culture taken from an intravenous catheter is incubated with radiolabeled ampicillin and then subjected to gel electrophoresis. The bands detected by autoradiography are most likely to represent which of the following?

A. Carboxypeptidases
B. Cell wall glycoproteins
C. Lipopolysaccharide
D. Lipoteichoic acid
E. Polysaccharide

2. A new laboratory technician forgets the iodine fixation step in a Gram stain of *Staphylococcus*. The organisms on the slide will:

A. Appear blue
B. Appear colorless
C. Appear pink
D. Dissolve
E. Wash off

3. If a culture is inoculated to a density of 3×10^2 cell/mL at time 0 and has both a generation and lag time of 10 minutes, how many cells/mL will there be in 40 minutes?

A. 1.2×10^3
B. 2.4×10^3
C. 4.2×10^3
D. 6×10^3
E. 3×10^6

4. A term male infant is delivered vaginally and without complications to a 23-year-old primigravida. While examining the baby at 36 hours of age, the physician notices that he is tachycardic, tachypneic, lethargic, and febrile. The mother explains that he has not been feeding well and is irritable when touched. Analysis of CSF fluid reveals elevated neutrophils and protein. Which of the following is the most likely cause of this infant's condition?

A. A gram-negative, oxidase-negative, lactose-fermenting bacillus
B. A gram-negative, oxidase-positive diplococcus
C. A gram-positive, catalase-negative, bacitracin-resistant coccus
D. A gram-positive, catalase-negative, optochin-sensitive coccus
E. A gram-positive, facultative-intracellular bacillus

5. A 3-year-old is brought to the ER for fever and difficulty breathing. When the physician walks in the room she notices that the child is drooling, sitting upright, and leaning forward. Lung exam shows stridor and retractions. X-ray reveals a thickened epiglottis. The vaccine that would have prevented this child's infection contains which of the following?

A. Capsular polysaccharide
B. Killed virus
C. Live virus
D. Polyribitol phosphate plus toxoid
E. Toxoid

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Review Questions Chapters 3–4

6. An immunocompromised person with a history of seizures had an MRI that revealed a temporal lobe lesion. Biopsy showed multinucleated giant cells with intranuclear inclusions. Which of the following describes the most likely pathogen?

A. dsDNA, enveloped, complex virus
B. dsDNA, enveloped, icosahedral virus
C. dsDNA, naked, icosahedral virus
D. dsRNA, naked, segmented virus
E. ssDNA, naked, icosahedral virus
F. ss(−)RNA, bullet-shaped helical virus
G. ss(−)RNA, naked, helical virus
H. ss(−)RNA, segmented, enveloped, and helical virus
I. ss(+)RNA, enveloped, diploid virus
J. ss(+)RNA, enveloped, icosahedral virus
K. ss(+)RNA, naked, icosahedral virus

7. A 16-year-old immigrant from Africa developed massive unilateral enlargement of his lower face in the region of the mandible. Biopsy of the lesion demonstrated sheets of medium-sized blast cells admixed with larger macrophages. Which of the following is the correct pairing of causal agent and mechanism of oncogenesis for this malignant lesion?

	Causal Agent	Mechanism of Oncogenesis
A.	Epstein-Barr virus	NFκB and Bcl2 activation
B.	Epstein-Barr virus	t(8;14)
C.	HHV-8	VEGF activation
D.	HTLV-1	p16/INK4a inactivation
E.	Human papilloma virus	P53 and Rb inactivation

8. A child with sickle cell anemia is seen in a hematology clinic. Her mother states that the child has been feeling very tired lately. The girl is very pale and a complete blood count shows severe anemia. A bone marrow aspirate is devoid of erythroid precursors. How does the most likely causal agent produce its mRNA?

A. A complementary strand of RNA is created using a viral polymerase
B. By transcription from its genome in the nucleus
C. By transcription from the provirus
D. By transcription from its genome in the cytoplasm
E. The viral genome is used as mRNA

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Chapters 3–4 Review Questions

9. A 4-month-old female was brought into the emergency room in severe respiratory distress, wheezing and with fever. Her symptoms began with cough and runny nose. Her physical exam showed a temperature of 39 degrees centigrade, a pulse of 200, and tachypnea with respiratory rate of 35 per minute. She had significant intercostal retractions and nasal flaring. A chest x-ray revealed interstitial infiltrates and hyperexpansion. The antiviral biological, which can be administered prophylactically to daycare contacts, acts by which of the following mechanisms?

A. Activation of an RNA endonuclease
B. Activation of a protein kinase that then inactivates eIF2
C. Blocking of the fusion protein
D. Blocking of the hemagglutinin protein
E. Blocking of the neuraminidase protein

10. A 25-year-old male is suffering from fatigue and jaundice. His laboratory workup is positive for HBsAg, positive for IgG antibody to HBcAg, positive for HBeAb, and negative for HBsAb. Which of the following is the most likely definition of his status?

A. Acute hepatitis B
B. Chronic hepatitis B
C. Convalescent from hepatitis B
D. Successfully vaccinated against hepatitis B
E. Window period of hepatitis B

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Review Answers Chapters 3–4

1. The correct answer is A. The question is asking where penicillin-style drugs bind to the bacterial cell. Penicillin-binding proteins are actually cell-wall synthesizing enzymes: carboxypeptidases and transpeptidases that are found in the cytoplasmic membrane. Although penicillins inhibit the formation of the cell wall cross-linkages, they do not exert their activity by binding in that location.

2. The correct answer is C. The iodine fixation step is the key step for the performance of the Gram stain. It serves as a complexing agent which binds the small crystal violet molecules to larger substances inside the cell. If this step were missed, then the gram-positive staphylococcal organisms would lose their purple color in the washing step just as if they were gram-negative and, at the end of the test, therefore, would appear pink.

3. The correct answer is B. There is no increase in bacterial number in the lag phase, but thereafter, bacteria will double every generation time. With a total of 40 minutes, the first 10 minutes is lag, and then there is enough time for 3 generations. Bacteria divide by binary fission, so the number of cells will double three times.

4. The correct answer is C. The most common cause of neonatal meningitis and septicemia is *Streptococcus agalactiae*, which is described as a gram-positive, catalase-negative, β-hemolytic, bacitracin-resistant and CAMP-test positive organism.

5. The correct answer is D. This child has *Haemophilus influenzae* epiglottitis which has been virtually eradicated from the U.S. with the use of a conjugate polysaccharide-protein vaccine. The capsular polysaccharide of *Haemophilus* is a polyribitol phosphate, and it is covalently coupled to the diphtheria toxoid, which acts as a protein carrier.

6. The correct answer is B. One-sided temporal lesions are typical of herpes simplex encephalitis. The herpes family of viruses are double-stranded DNA, enveloped, and icosahedral.

7. The correct answer is B. The patient most likely has Burkitt lymphoma, which results from a translocation of the c-myc oncogene next to the very active promoter region for immunoglobulin synthesis.

8. The correct answer is B. The child is likely infected with parvovirus B19, which is a single-stranded DNA virus. It moves to the nucleus after it enters the cell and allows cellular transcriptases to produce its mRNA.

9. The correct answer is C. The child is likely infected with respiratory syncytial virus, which is a paramyxovirus distinguished by the presence of a lone fusion protein on its surface. Palivizumab is the monoclonal against RSV fusion protein which can be administered prophylactically to high-risk groups.

10. The correct answer is A. Since the patient is symptomatic, positive for HBsAg and IgG against HBcAg, he is probably in the later stages of the acute infection. He has developed antibodies against the HBeAg so he is not highly contagious.

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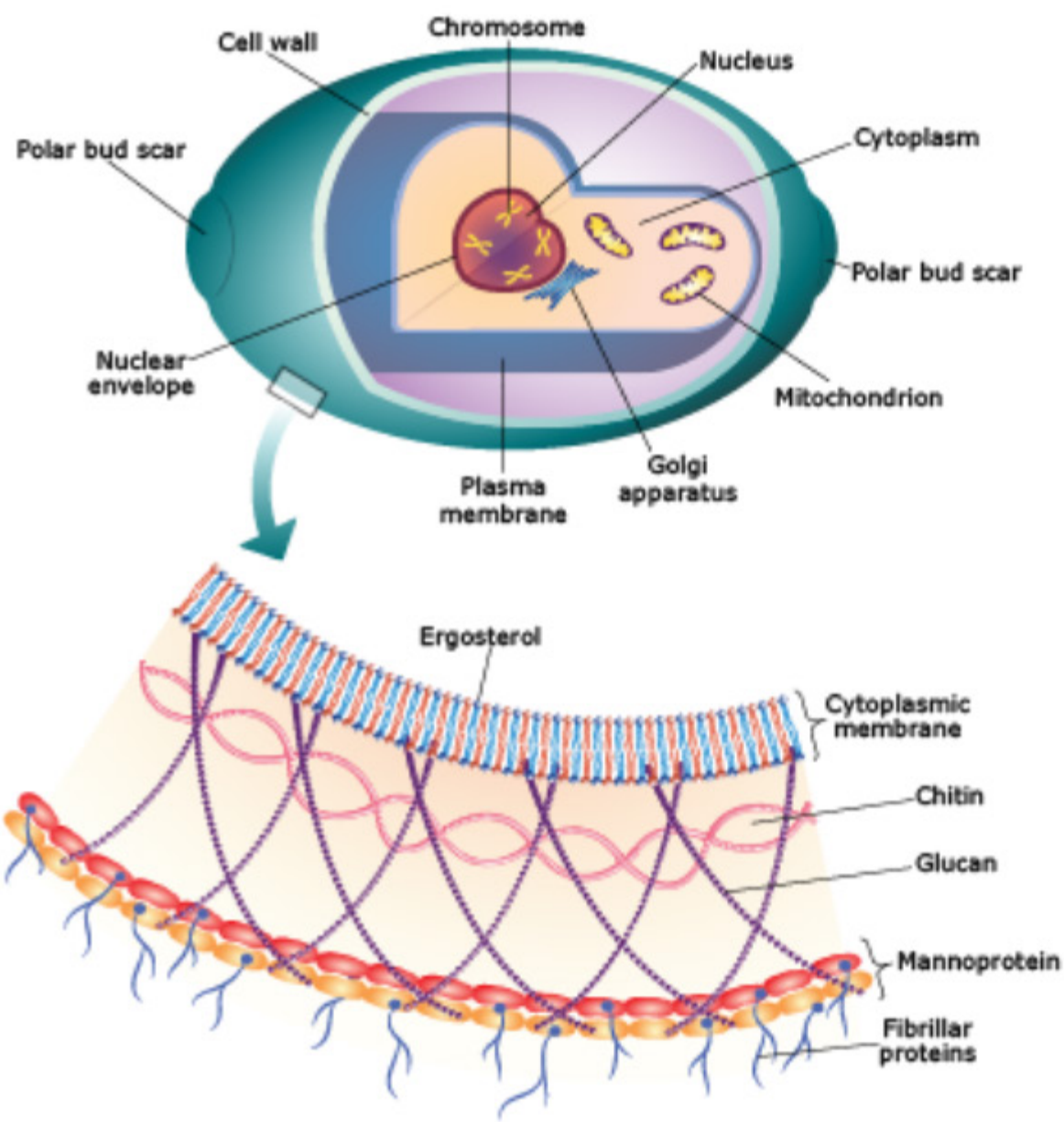
1 Biology of Fungi

1.1 Structure

Fungi are *eukaryotic*, with all the typical cellular organelles. They differ from all other eukaryotes in that they:

- Possess a rigid cell wall containing *mannan*, *glucan*, and *chitin*.
- Have *ergosterol* as their major membrane sterol.



▲ **Figure 5-1.1** Anatomy of Yeast Cell

USMLE® Key Concepts

For Step 1, you must be able to:

- Identify and describe the basic structures of fungi from microscopic images.
- Distinguish the structure, chemistry, and physiology of the fungi from other microorganisms.
- Diagnose and recommend therapies for the common fungal pathogens in the U.S.
- Explain the mechanisms of action of the major anti-fungal drugs.

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1.2 Physiology and Metabolism

Fungi are *heterotrophic*, requiring organic substrates as an exogenous source of carbon. Most fungi are aerobic.

1.3 Reproduction

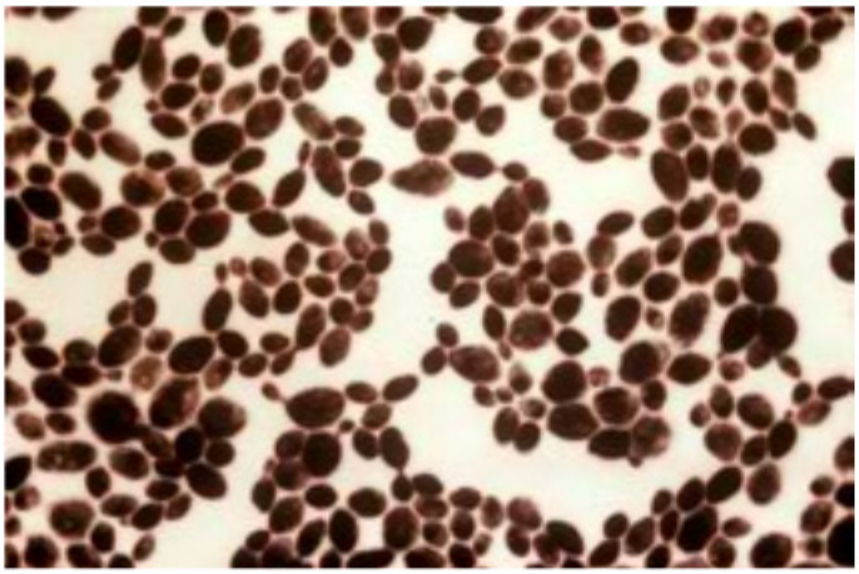
Fungal reproduction may be asexual or sexual.

- Asexual reproductive elements: *Conidia.*
  - Conidia that form exogenously: *Macroconidia* and *microconidia.*
  - Conidia that form within the hypha: *Arthroconidia* (conform to shape of hypha with "joints" to break loose).
- Sexual reproductive elements: *Ascospores*, *basidiospores*, and *zygospores.*
- Spores: Specialized sexual or asexual reproductive forms with enhanced survival in the environment.

1.4 Morphology

1.4.1 Yeasts

Yeasts are single-celled fungi that grow by extension, constriction, and separation of new cells from the parent. The buds formed in this way are called *blastoconidia*.



Science VU/Visuals Unlimited, Inc.

▲ **Figure 5-1.4** Yeasts

1.4.2 Molds

The growth of fungi through the development of apical tube-like extensions generates *hyphae*. An intertwined mass of hyphae is called a *mycelium*, and organisms that grow in this fashion are typically called *molds*. Most fungal hyphae develop with *septae*, cross-walls perpendicular to the cell walls dividing the cell into subunits. *Non-septate hyphae* grow as a single, continuous cell with irregularly wide filaments and without regular cross-walls.

Memory Aid

Remember the key U.S. dimorphic fungal pathogens with the following mnemonic:

Body **H**eat **C**hanges **S**hape (***B**last**o**myces*, ***H**istoplasma*, ***C**occidioides*, and ***S**porothrix*).

Additionally, remember two phrases: *Mold in the cold; yeast in the beast* to recall which form the fungi take in each environmental situation. *Paracoccidioides* is also dimorphic, but is not endemic to the U.S.

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1.4.3 Pseudohyphae

Some fungi produce *pseudohyphae* that form as buds that become elongated and fail to detach from the parental yeast cell.

1.4.4 Dimorphic Fungi

Some fungal species can grow in yeast or hyphal phase depending on environmental conditions. These are referred to as *dimorphic fungi.* At room temperatures they tend to be hyphal, while in the tissues they convert to yeasts or a yeast-like stage. This is a complex physiologic conversion that is reversible, and therefore not a developmental process, as is seen in higher eukaryotes.

Clinical Application

Because filamentous fungi grow apically, it is important to sample fungal skin lesions for diagnosis from the leading edge in the active growing margin.

1.5 Diagnosis

1.5.1 Direct Examination

- Scraping or biopsy treated with KOH that digests mammalian cells and leaves the complex carbohydrate cell wall of fungi intact.
- Special stains:
  - Calcofluor-white: Cellulose and chitin will fluoresce.
  - Gram stain: Yeasts such as *Candida* are gram-positive.
  - Silver stains: Darken polysaccharide components of fungal cell walls.
  - India ink:
    - Insensitive test of CSF for encapsulated cryptococcal yeasts.
    - Particulate dye deposits around yeasts, does not penetrate capsular polysaccharide, shows capsular halo.
    - Misses 50% of infections: Can only "rule in" if positive; now supplanted by latex particle agglutination test for capsular antigens.

1.5.2 Culture

Fungi are slow growing, but Sabouraud agar is most commonly used. Yeasts are further differentiated by biochemical tests, and molds are identified by the morphology of their conidia.

1.5.3 Serology

Not sufficiently specific or sensitive for use.

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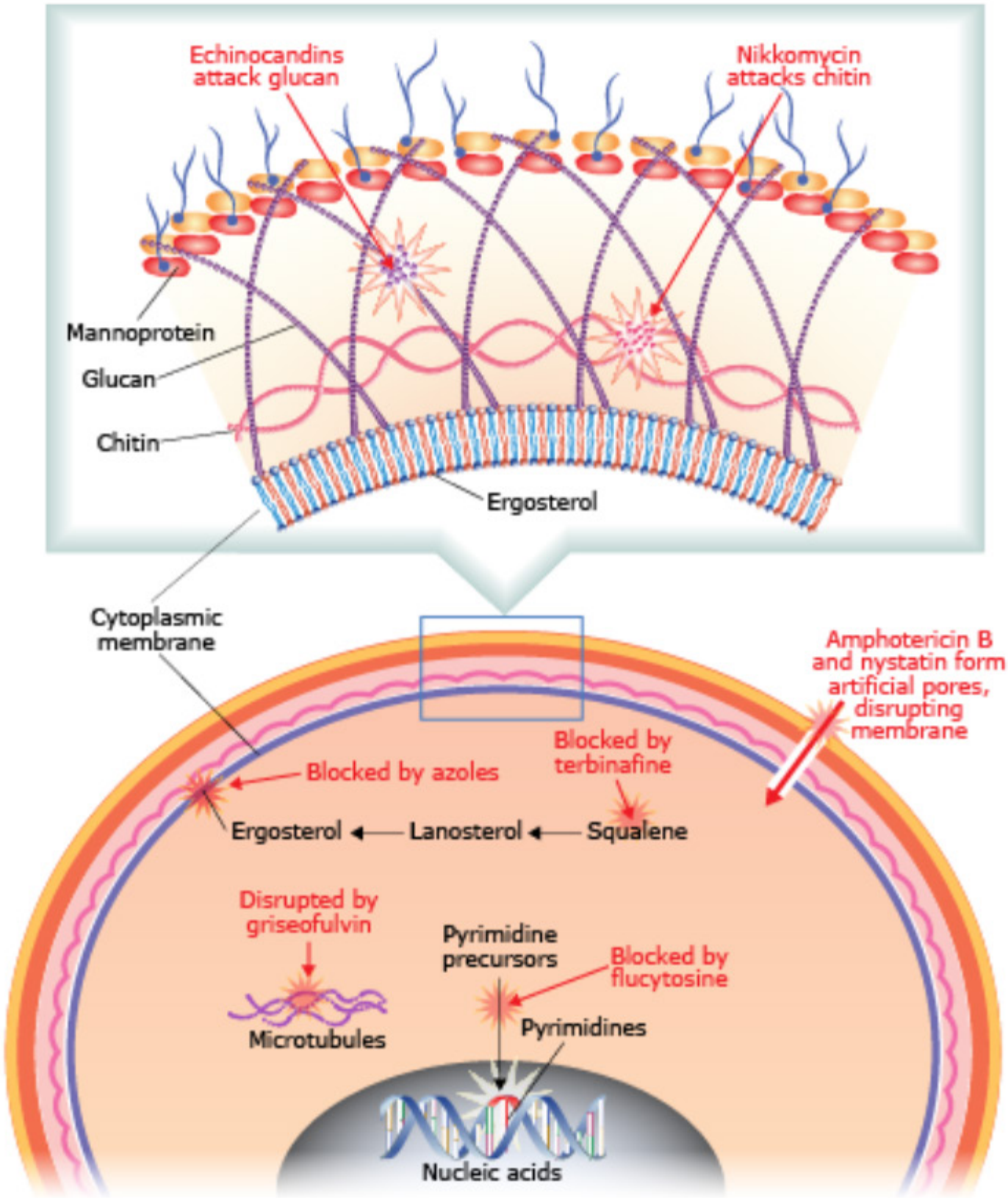
1.6 Mechanism of Action of Major Antifungals



▲ **Figure 5-1.6** Action of Antifungal Agents

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2 Superficial and Subcutaneous Mycoses

2.1 Keratinized Tissues

2.1.1 *Malassezia furfur*

Characteristics

- Lipophilic yeast
- Normal skin flora

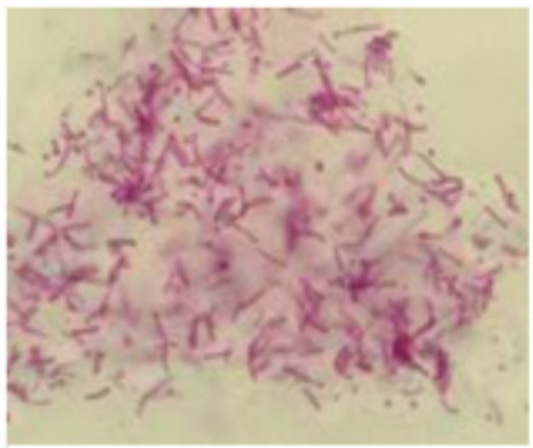
Clinical Syndrome

- Pityriasis (tinea) versicolor: Blotchy hypopigmentation of skin of chest and back (sometimes hyperpigmentation)
- Fungemia in premature infants on intravenous lipids

Diagnosis

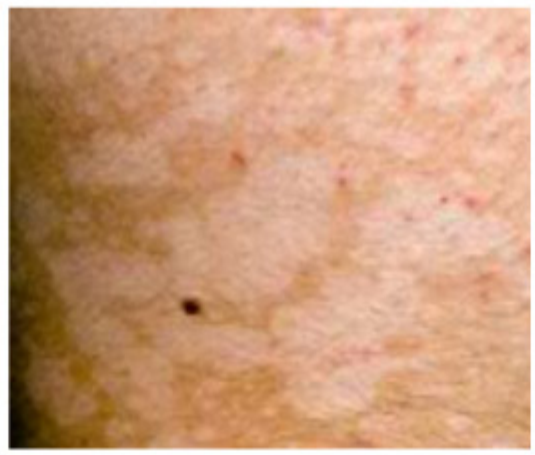
- Wood's lamp (UV light): Coppery fluorescence
- KOH skin scraping: Round yeast clusters and short, curved septate hyphae ("spaghetti and meatballs")

Treatment Selenium sulfide topically



CDC/Dr. Lucille K. Georg

▲ **Figure 5-2.1A** KOH Preparation of *Malassezia* Skin Scraping



Dr. P. Marazzi/Science Source

▲ **Figure 5-2.1B** Pityriasis Versicolor

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2.2 Cutaneous Infections (Dermatophytoses)

2.2.1 *Microsporum* spp., *Trichophyton* spp., and *Epidermophyton* spp.

Characteristics

- Monomorphic, filamentous fungi
- Transmitted from fomites or human-to-human through minor abrasions
- *Trichophyton* spp. infect skin, hair and nails
- *Epidermophyton* spp. infect skin and nails
- *Microsporum* spp. infect skin and hair

Clinical Syndrome Tinea ("ringworm")

- Tinea capitis: Scalp
- Tinea corporis: Trunk
- Tinea cruris: Jock itch
- Tinea pedis: Athlete's foot
- Tinea unguium (onychomycosis): Infection of the nail bed

Biophoto Associates/Science Source

▲ **Figure 5-2.2A** Tinea Capitis

Scott Camazine/Science Source

▲ **Figure 5-2.2B** Tinea Corporis

Harout V. Tanielian/Science Source

▲ **Figure 5-2.2C** Tinea Cruris

Science Source

▲ **Figure 5-2.2D** Tinea Unguium

Diagnosis

- Clinical: Pruritic, circular lesions on the skin, some fluoresce with Wood's lamp
- Skin scraping treated with KOH: Septate hyphae

Treatment

- Topical tolnaftate or azoles
- Nail bed and hair shaft infections: Systemic griseofulvin, itraconazole, terbinafine

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2.3 Subcutaneous Mycoses (Eumycotic Mycetomas)

2.3.1 *Sporothrix schenckii*

Characteristics Dimorphic

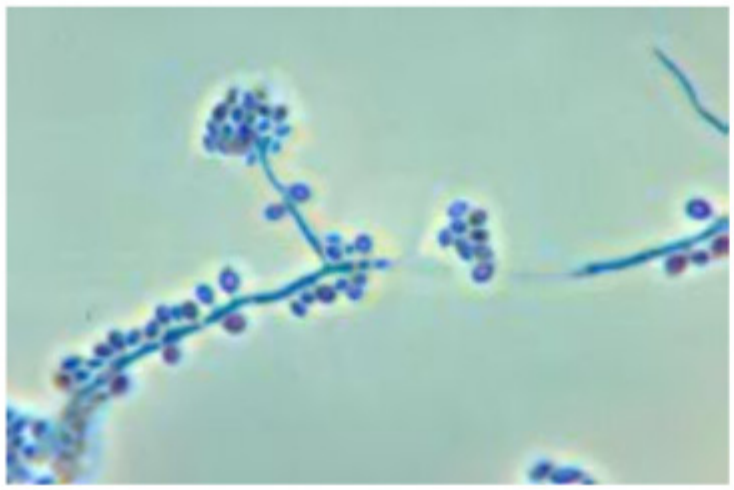
- Environmental form: Worldwide on plant material, hyphae with rosettes and sleeves of conidia
- Diagnostic form: Cigar-shaped yeast in tissue

Clinical Syndromes

- **Rose Gardener's Disease:** Subcutaneous or lymphocutaneous mycetoma resulting from trauma while gardening
- **Pulmonary Sporotrichosis:**
  - Acute or chronic
  - Homeless, alcoholics inhaling infectious forms

Diagnosis Culture of tissue or sputum

Treatment Itraconazole or amphotericin B



Courtesy of the Centers for Disease Control

▲ **Figure 5-2.3A** Infectious Form of Sporothrix schenckii

Medicimage/Visuals Unlimited, Inc.

▲ **Figure 5-2.3B** Rose Gardener's Disease

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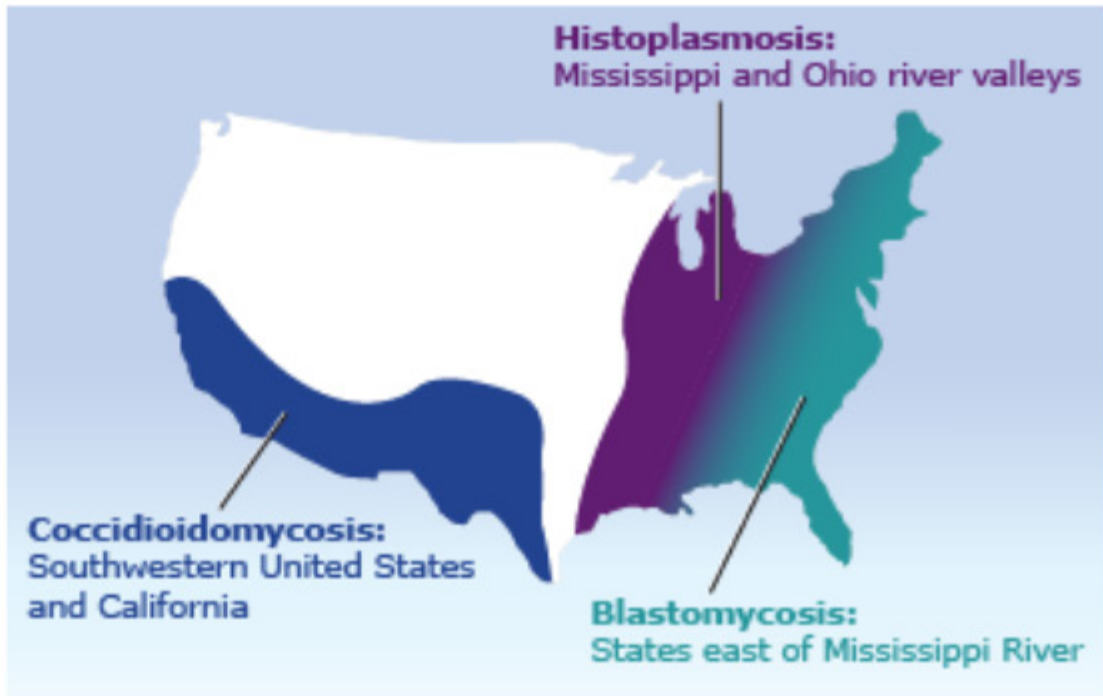
3 Systemic Mycoses

The systemic mycoses, sometimes referred to as the classical fungal pathogens, are all—except *Paracoccidioides*, which occurs in South and Central America—problems in AIDS patients in the U.S. They are all believed to be transmitted via inhalation. They may cause similar clinical presentations: acute pulmonary, chronic pulmonary, or disseminated infections. They are distinguished by microscopic examination of sputum or lesions, and may also be distinguished by their geographic incidence.



▶ **Figure 5-3.0** Geographic Distribution of Systemic Mycoses in the U.S.

3.1 *Blastomyces dermatitidis*

Characteristics Dimorphic

- Tissue form is a large yeast with broad-based buds and a thick cell wall
- Environmental form: Septate hyphae with round to oval conidia
- Geographic incidence coincides with histoplasmosis, but also includes Atlantic seaboard states (North Carolina and South Carolina) and goes north through Minnesota into Canada

Clinical Syndrome Blastomycosis

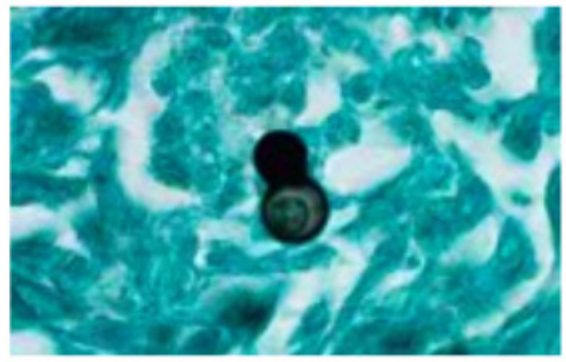
- Acute or chronic pulmonary (productive cough, chest pain, fever)
- Skin lesions on exposed skin, necrosis and fibrosis

Diagnosis KOH preparation of sputum or skin lesion, broad-based budding yeasts

Treatment Itraconazole or amphotericin B

CDC/Dr. Martin Castro, San Paulo, Brazil/ Dr. Lucille K. Georg

▲ **Figure 5-3.1A** Dissemination of *Blastomyces* to the Skin



Dr. Gladden Willis/Visuals Unlimited, Inc.

▲ **Figure 5-3.1B** *Blastomyces* Budding Yeast

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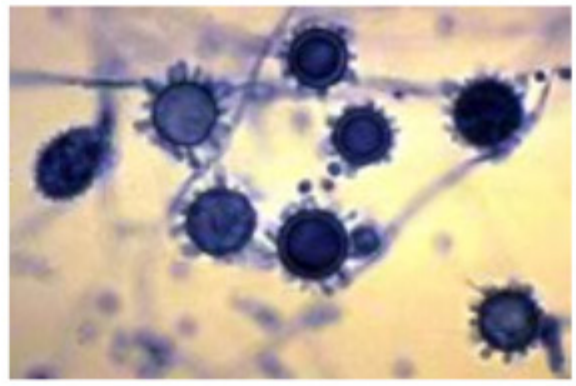
3.2 *Histoplasma capsulatum*

Characteristics

- Dimorphic, facultative intracellular
- Tissue form is small intracellular yeast with clear halo around it (not a capsule, but a shrinkage artifact)
- Environmental form: Septate hyphae with microconidia and tuberculate (thick wall with radial finger-like projections) macroconidia
- Geographic incidence: Follows the drainage basins of the Great Lakes and the Mississippi and Ohio rivers to the Gulf of Mexico
- Found in high numbers in chicken coops or bat roosts in endemic area



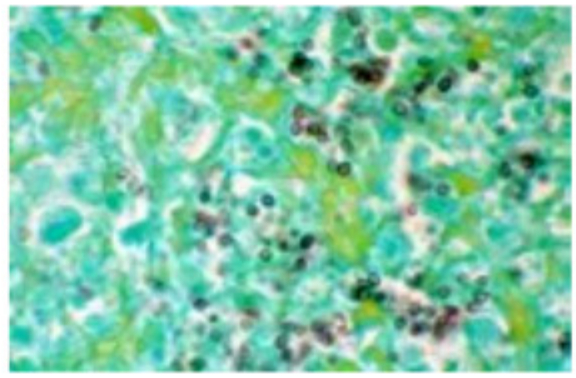
Science Source

▲ **Figure 5-3.2A** Environmental Form of *Histoplasma capsulatum*

Clinical Syndrome Histoplasmosis, "fungus flu"

- Asymptomatic to acute or chronic pulmonary (productive cough, chest pain, fever); severity depends on infectious dose and patient health status
- Mediastinal lymphadenopathy, hepatosplenomegaly, and calcifying lesions on radiograph
- Disseminated disease produces painless ulcers on mucous membranes

Diagnosis Histologic examination of biopsy with methenamine silver stain, thick blood smear with Giemsa stain or blood culture for small intracellular yeasts



SB Lucas/Wellcome Images

▲ **Figure 5-3.2B** Tissue Form of *Histoplasma capsulatum*

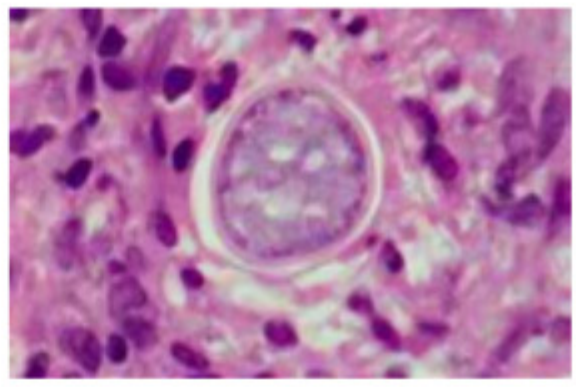
Treatment

- Most cases in healthy patients resolve with rest and supportive care
- Itraconazole, amphotericin B
- Prophylaxis in AIDS begun with itraconazole at 100 CD4 cells/μl in endemic area

3.3 *Coccidioides immitis*

Characteristics

- Dimorphic: Tissue form is large, round-walled spherule containing multiple, uninucleate endospores
- Environmental form: Septate hyphae with arthroconidia
- Geographic incidence: Alkaline soils of semi-arid desert areas (Sonoran Desert of California, Arizona, New Mexico, and Texas), disrupted by wind storms



Michael Abbey/Science Source

▲ **Figure 5-3.3A** *Coccidioides* Spherule

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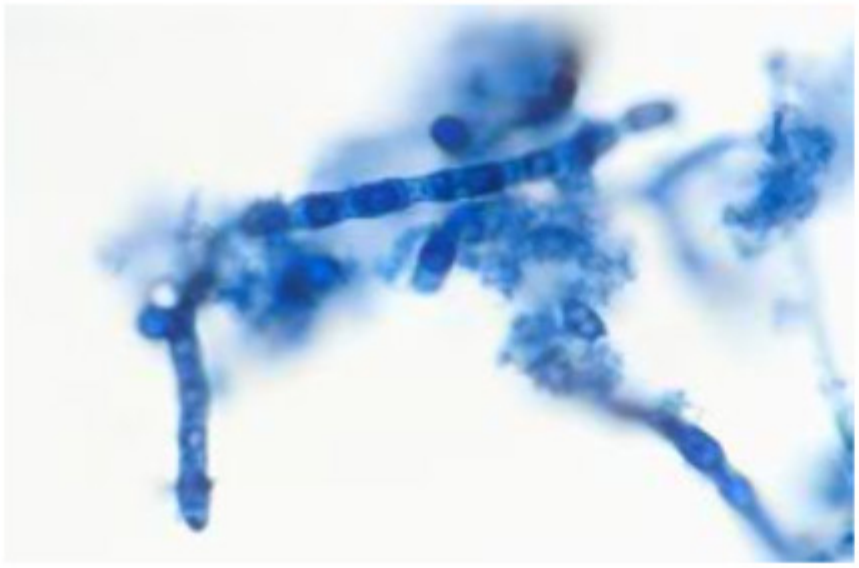
Clinical Syndromes Coccidioidomycosis, Valley fever, San Joaquin Valley fever

- Asymptomatic to acute or chronic pulmonary with cough, chest pain, fever, and arthralgia
- Erythema nodosum, or desert bumps: Common in endemic area, indicate a strong immune response
- Dissemination to bones, joints, skin, and meninges in AIDS patients
- Risk of dissemination in third trimester of pregnancy

Diagnosis Biopsy or wet mount treated with KOH and stained with calcofluor-white: Large, thick-walled spherules

Treatment Self-limiting in patients with normal immunity; AIDS and other compromised patients such as diabetics require amphotericin B and an azole



Michael Abbey/Visuals Unlimited, Inc.

▲ **Figure 5-3.3B** Arthroconidia of *Coccidioides*

3.4 *Paracoccidioides brasiliensis*

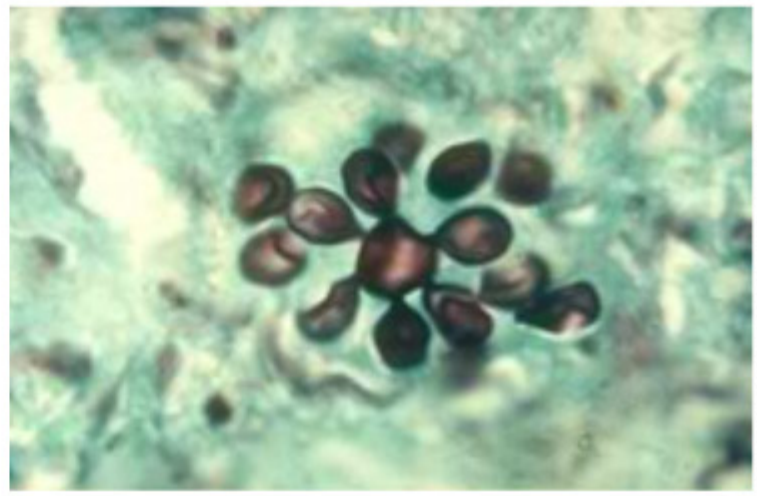
Characteristics

- Dimorphic fungus
- Tissue phase is a yeast with multiple blastoconidia produced on the same yeast cell creating the appearance of a "captain's wheel"
- Geographic incidence: Tropical and subtropical areas of Central and South America

Clinical Syndromes Paracoccidioidomycosis, South American blastomycosis: Chronic mucocutaneous or cutaneous ulcers

Diagnosis Tissue biopsy, KOH and calcofluor, multiple-budding blastoconidia

Treatment Sulfonamides, amphotericin B, and azoles



Courtesy of the Centers for Disease Control

▲ **Figure 5-3.4** *Paracoccidioides* Tissue Form

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4 Opportunistic Mycoses

4.1 *Cryptococcus neoformans*

Characteristics

- Monomorphic, encapsulated yeast
- Antiphagocytic polysaccharide capsule
- Urease positive
- Transmitted via inhalation from soil enriched with bird droppings, especially pigeons, turkeys, and chickens

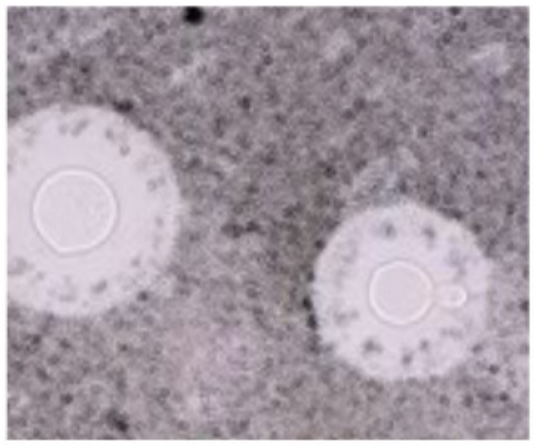
Clinical Syndromes

- **Meningitis:** Insidious onset, headache, irritability, behavioral changes, seizures, fever
- **Pneumonia:** Asymptomatic or mild, atypical

Diagnosis

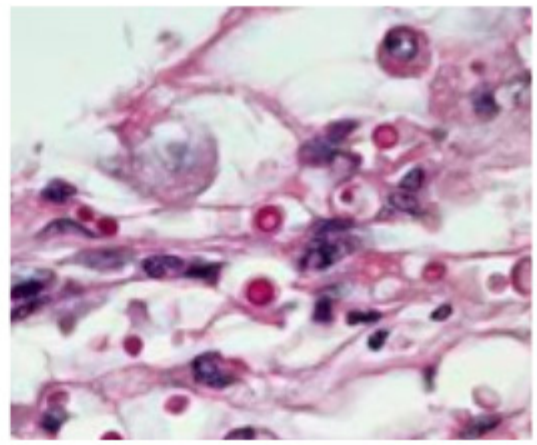
- 50% of patients may have organisms demonstrable in sediment of CSF mixed with India ink
- Latex particle agglutination to detect capsular polysaccharide in CSF

Treatment Amphotericin B plus flucytosine, followed by an extended course of fluconazole



Dr. Gladden Willis/Visuals Unlimited, Inc.

▲ **Figure 5-4.1A**
India Ink Preparation of *Cryptococcus neoformans*



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▲ **Figure 5-4.1B**
Cryptococcus neoformans Encapsulated Yeasts in Tissue

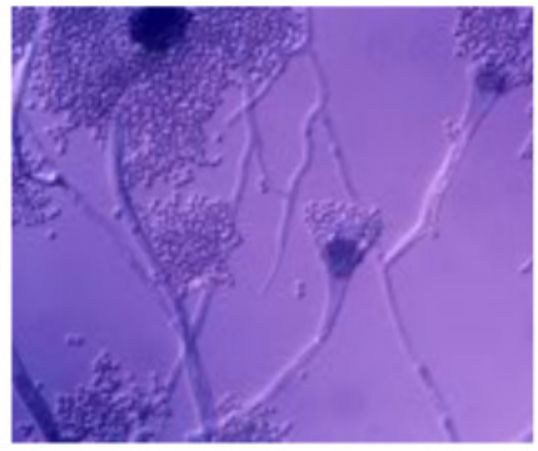
4.2 *Aspergillus fumigatus*

Characteristics

- Monomorphic filamentous fungus with septate hyphae
- Branches dichotomously and at acute angles
- Conidia are acquired by inhalation from the environment

Clinical Syndromes

- Allergic aspergillosis exacerbates asthma and cystic fibrosis; allergen is growing in mucus plugs in the lungs, not in the tissue
- Invasive aspergillosis in severely immunocompromised: Tissue invasion causing acute pneumonia or colonization of sinus surfaces with direct extension to the CNS
- Aspergilloma: Spores germinate in preexisting cavitary lesions and grow apically with branches forming a mycelial mass called a fungus ball



Daniel Snyder/Visuals Unlimited, Inc.

▲ **Figure 5-4.2**
Aspergillus Conidiophores and Conidia

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Diagnosis

- Lung aspiration, biopsy or lavage
- Uniformly branching septate hyphae

Treatment

- Voriconazole, itraconazole, caspofungin, amphotericin B
- Surgical resection of fungus balls

4.3 *Candida albicans*

Characteristics

- Budding round to oval yeasts as normal flora of mucous membranes
- Pseudohyphae: Elongated forms with constrictions at intervals

Pathogenesis

- Pseudohyphae and hyphae formed by invasive strains
- Morphologic changes are marked by the appearance of factors associated with tissue adherence and digestion
- Hyphal wall protein (Hwp1) mediates binding
- Hyphae secrete proteinases and phospholipases that facilitate invasion

Clinical Syndromes

Biophoto Associates/Science Source

▲ **Figure 5-4.3A** *Candida albicans*: Thrush

▼ **Table 5–4.3** *Candida albicans*: Clinical Syndromes

Patient Predisposition	Candidal Growth	Treatment
Premature infant, antibiotic use, immunocompromised	Thrush (overgrowth in the mouth)	Nystatin, azoles
AIDS	Esophagitis, gastritis	Fluconazole, amphotericin B, caspofungin
Immunocompromised, cancer, and IV patients	Septicemia	Fluconazole, amphotericin B, caspofungin
IV drug users	Endocarditis	Fluconazole, amphotericin B, caspofungin
Infants, patients who must wear rubber gloves, obese patients	Cutaneous infections, diaper rash	Nystatin, azoles, keep skin dry
Diabetic women	Vaginitis	Nystatin, azoles
Patients with specific Th1 defect or diabetes	Chronic mucocutaneous candidiasis	Fluconazole

Diagnosis Germ tube test: Observe formation of hyphae from yeasts in animal serum at 37°C

Custom Medical Stock Photo

▶ **Figure 5-4.3B** Germ Tube Test

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4.4 Zygomycosis (*Mucor, Rhizopus, Absidia*)

Characteristics

- Saprophytes in soil, commonly found on bread and other food
- Infection by inhalation of conidia
- Ribbon-like, irregular width, nonseptate hyphae
- Branch at 90° angles

Clinical Syndrome Rhinocerebral infection

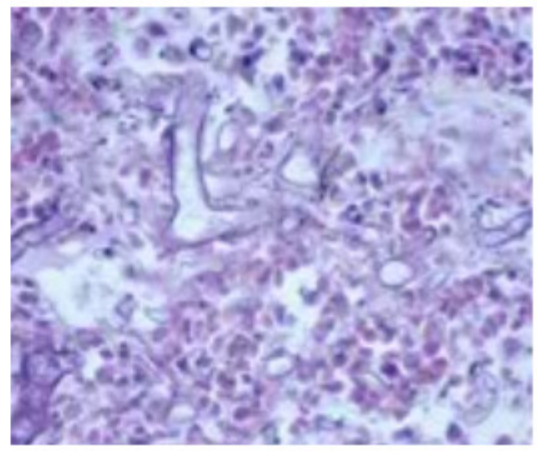
- Immunosuppressed patients on corticosteroid therapy or diabetics with acidosis
- Headache, orbital cellulitis, hemorrhage, cranial nerve palsy, coma, rapid death

Diagnosis Tissue biopsy, KOH treatment, and fungal stain

Treatment Control of underlying disease, surgery, amphotericin B

Custom Medical Stock Photo

▲ **Figure 5-4.4 A**
Zygomycosis



CNRI/Science Source

▲ **Figure 5-4.4 B**
Ribbon-Like Hyphae of Zygomycophyta

4.5 *Pneumocystis jirovecii*

Characteristics

- Classified as a fungus by ribosomal RNA analysis
- Major membrane sterol is cholesterol
- Cell wall is thin, but contains chitin and glucan
- Cannot be cultured

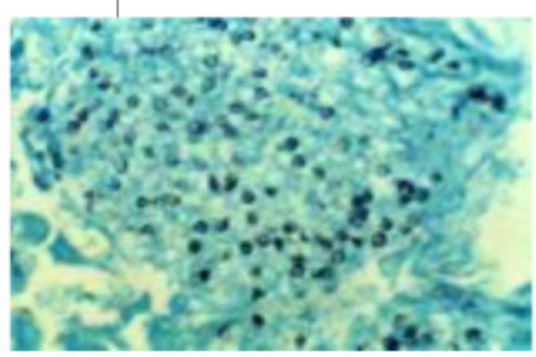
Clinical Syndrome

- Atypical pneumonia in premature infants and AIDS patients
- Attaches to and kills type I pneumocytes, causes type II pneumocytes to replicate
- Alveoli fill with dense exudate
- Death by asphyxiation

Diagnosis

- Biopsy or lavage necessary
- Small, silver staining cyst-like structures found in "honeycomb-like" exudate

Treatment Trimethoprim-sulfamethoxazole; start AIDS patients on prophylaxis when CD4 count falls below 200/µL



Mary Ruebush

▲ **Figure 5-4.5**
Pneumocystis Honeycomb Exudate

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1 Biology of Parasites

Parasites are the most diverse group of organisms that cause human disease. They range from single-celled *protozoa*, classified by their modes of motility, to multicellular *metazoa*, classified by their complex anatomical features.

1.1 Protozoan Parasites

▼ **Table 6–1.1** Protozoan Parasites

Category	Characteristics	Genera
Amebae	• Motility by pseudopodia • Life cycle includes trophozoite (feeding form) and cyst (resistant transmission form)	• *Acanthamoeba* • *Entamoeba* • *Naegleria*
Ciliates	• Motility by cilia • Life cycle involves trophozoite and cyst	• *Balantidium*
Flagellates	• Motility by flagella • Gastrointestinal and urogenital forms alternate between trophozoite and cyst • Hemoflagellates have non-flagellated (amastigote) and flagellated (trypomastigote) forms	• *Giardia* • *Leishmania* • *Trichomonas* • *Trypanosoma*
Sporozoa/ apicomplexa	• Intracellular in the human • Penetrate cells using an apical complex	• *Babesia* • *Cryptosporidium* • *Isospora* • *Plasmodium* • *Toxoplasma*

USMLE® Key Concepts

For Step 1, you must be able to:

- Diagnose and treat the major parasitic diseases.
- Describe the means of infection for the major parasites.
- Identify the scientific and common names for parasites and their diseases.
- Explain the relationship between the *Plasmodium* life cycle and the pathogenesis of malaria.

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1.2 Metazoan Parasites

▼ **Table 6–1.2** Metazoan Parasites

Phylum	Class	Characteristics	Genera
Nemathelminthes	Nematoda	• Round in cross-section • Complete digestive tract • Separate sexes • Simple life cycles alternate between egg, larva, and adult	• *Ancylostoma* • *Ascaris* • *Brugia* • *Dracunculus* • *Enterobius* • *Loa* • *Necator* • *Onchocerca* • *Strongyloides* • *Toxocara* • *Trichinella* • *Trichuris* • *Wuchereria*
Platyhelminthes	Cestoda	• Flattened in cross-section • No digestive tract • Hermaphroditic • Complex life cycles have egg, larvae, and adults in separate hosts	• *Diphyllobothrium* • *Echinococcus* • *Taenia*
	Trematoda	• Flattened in cross-section • Incomplete digestive tract (no anus) • Hermaphroditic (except schistosomes) • Complex life cycles have egg, larvae, and adults in separate hosts	• *Clonorchis* • *Fasciola* • *Fasciolopsis* • *Paragonimus* • *Schistosoma*

1.3 Hosts

The organism that harbors the adult or sexual stages of the parasite is known as the *definitive host*. The organism that harbors larval or asexual stages of the life cycle is referred to as the *intermediate host*.

1.4 Antiparasitic Drugs

▼ **Table 6–1.4** Antiparasitic Drugs

Drug	Mechanism of Action	Use
Iodoquinol	Halogenated quinolone; unknown	Amebiasis
Paromomycin	Aminoglycoside	Cryptosporidiosis
Chloroquine	Inhibits the degradation of hemoglobin	Malaria, acute attack
Primaquine	8-aminoquinolone, may generate reactive oxygen species or interfere with the electron transport system	Malaria (*P. vivax* or *P. ovale*), radical cure
Suramin	Inhibits glycerophosphate oxidase and dehydrogenase	African trypanosomiasis
Benznidazole	DNA binder	Chagas disease
Stibogluconate	Pentavalent antimonial, unknown	Leishmaniasis
Mebendazole	Inhibits polymerization of microtubules	*Intestinal nematode infections*
Thiabendazole	Unknown, inhibits fumarate reductase (?)	Strongyloidiasis, cutaneous larva migrans, visceral larva migrans, trichinosis
Diethylcarbamazine	Neuromuscular paralysis	Filariasis
Ivermectin	Binds to glutamate-gated chloride channels	Filariasis
Praziquantel	Unknown; may increase permeability of membranes toward calcium ions	*Trematode and cestode infections*

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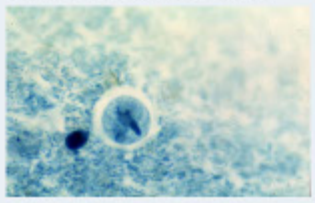
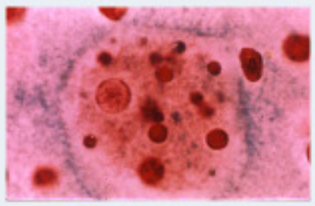
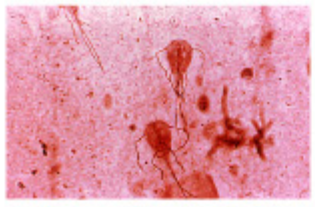
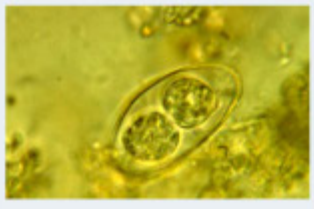
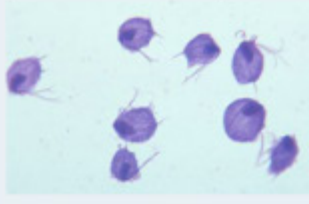
2 Protozoa

2.1 Mucosal (Gastrointestinal or Urogenital) Protozoa

▼ **Table 6–2.1** Mucosal Protozoa

Organism & Disease	Pathogenesis	Key Vignette Clues	Diagnosis	Treatment
Fecal-oral transmission of cyst stage				
Entamoeba histolytica (amebic dysentery)  Cyst  Trophozoite	Amebae invade colon, create inverted flask-shaped lesions, may spread via blood to liver	*Travel to Mexico* or tropics, blood and pus in stool, fever, may produce liver abscesses	Stool: cysts with 1–4 nuclei and/or trophozoites, rapid stool antigen test, serology for hepatic abscess	Metronidazole with diloxanide
Giardia lamblia (giardiasis)  Trophozoites	Trophozoites attach to small intestinal mucosa, block entry of small bile ducts	Patient has been *camping or hiking;* foul-smelling, fatty, bulky diarrhea	Trophozoites or cysts in fresh feces, trophozoites with *falling leaf motility*	Metronidazole
Cryptosporidium parvum (cryptosporidiosis) 	Obligate intracellular	Explosive diarrhea in immunocompetent, lasts 5–10 days; AIDS: indolent and persistent	Acid-fast oocysts in stool	Self-limiting in normal patients; paromomycin in immunocompromised patients
Isospora belli (isosporiasis)	Obligate intracellular	Similar to *Cryptosporidium*	Acid-fast oocysts in stool	Self-limiting except in AIDS
Sexual transmission of trophozoite stage				
Trichomonas vaginalis (trichomoniasis) 	Sexual	Vaginitis after menses; thin, yellow, frothy discharge; males generally asymptomatic	Flagellate in vaginal (or urethral) smear, *corkscrew motility*	Metronidazole, contact tracing

1.–3. Mary Ruebush; 4. A. Moody/Wellcome Images; 5. Carolina Biological Supply, Co/Visuals Unlimited, Inc.

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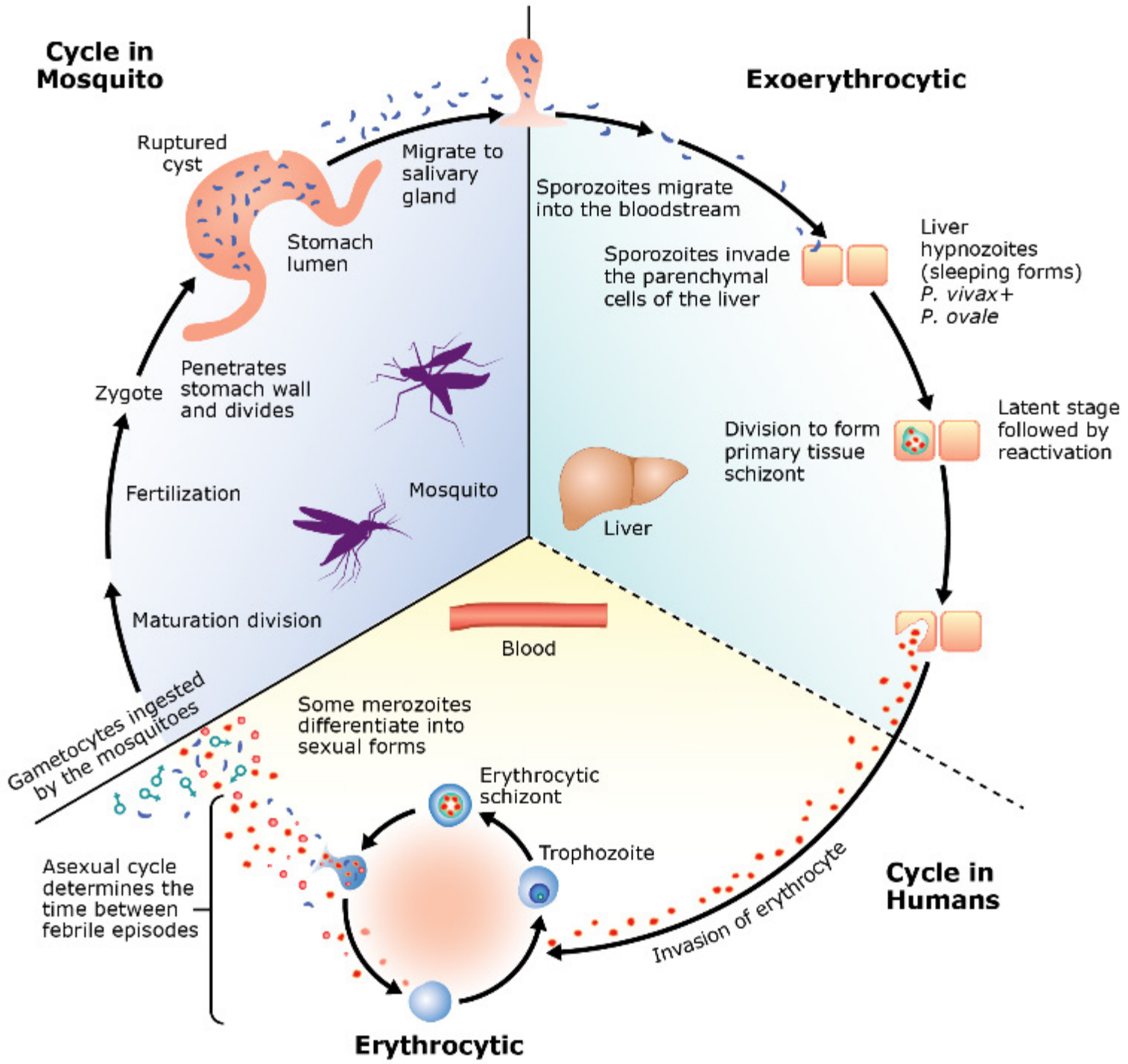
2.2 Blood and Tissue Protozoa

2.2.1 *Plasmodium* spp. (Malaria)

Characteristics

- Intraerythrocytic sporozoan parasite
- Sexually reproductive forms occur in the mosquito (definitive host)
- Asexual reproduction occurs in the human (intermediate host)

Transmission Bite of the female *Anopheles* mosquito with injection of sporozoites



▲ **Figure 6-2.2A** *Plasmodium* Life Cycle

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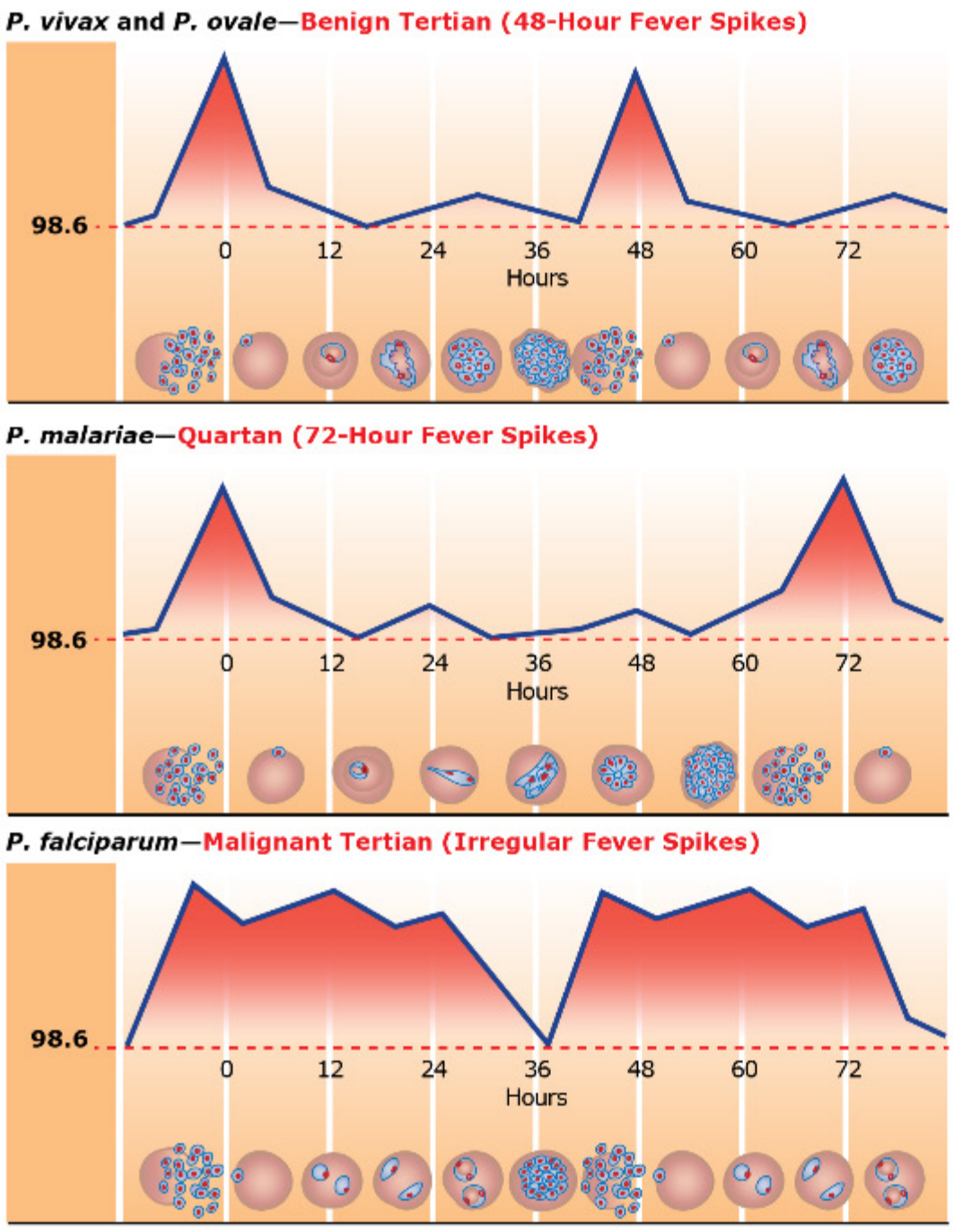
Pathogenesis

- There is no pathology or symptomatology associated with the exoerythrocytic phase of the life cycle.
- Once erythrocytes begin to be lysed in a cyclical fashion, spikes of fever will occur with each crop of RBCs lysed.
- The fever drops as the parasites enter new red blood cells and the cycle repeats.
- Lysis of RBCs and dumping of malarial pigment (hemozoin) into the blood cause reticuloendothelial congestion, hemolytic anemia, and even kidney failure.
- *P. falciparum* causes infected RBCs to adhere to the endothelia of visceral capillaries, impairing microcirculation, causing tissue hypoxia, lactic acidosis, and hypoglycemia (cerebral malaria).

Clinical Syndrome

- Chills, fever, splenomegaly, and anemia
- Malarial paroxysm: Synchronized lysis of RBCs causes rigors, fever of 40–41.7°C, and diaphoresis, repeated in 48- or 72-hour cycles



▲ **Figure 6-2.2B** Patterns of Malarial Fevers

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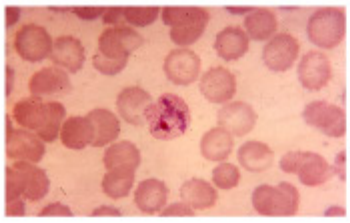
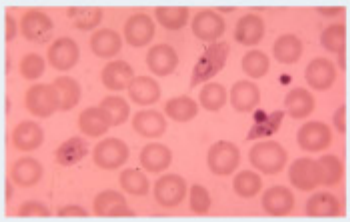
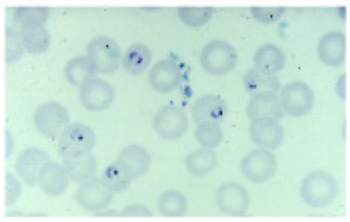
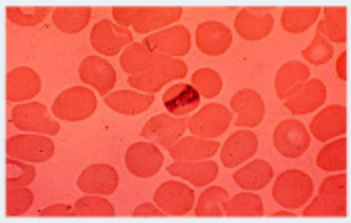
Diagnosis

▼**Table 6–2.2A** Diagnosis of *Plasmodium* Species

Species	Diagnosis	Treatment
Plasmodium vivax (85% of all cases worldwide) 	48-hour fever spikes, infected RBC are enlarged, trophozoite highly ameboid	Chloroquine followed by primaquine (radical cure to destroy hypnozoites and prevent relapse)
P. ovale 	48-hour fever spikes, infected RBC are distorted or oval	Chloroquine followed by primaquine (radical cure to destroy hypnozoites and prevent relapse)
P. falciparum (95% of all malarial deaths) 	Irregular fever pattern, infected RBCs are small and multiply infected	Chloroquine resistance is a problem, no radical cure necessary, recrudescence possible due to global drug resistance
P. malariae 	72-hour fever spikes, infected RBC are normocytic, may have band forms	Chloroquine, no radical cure, but recrudescence may occur from inadequate therapy

1.–4. Mary Ruebush

Prophylaxis

- Mefloquine or doxycycline
- Natural immunity
  - HbS heterozygote is protected from *P. falciparum*
  - Duffy blood group–negative: Cannot be infected with *P. vivax*
  - Thalassemic and other abnormal hemoglobins: Indigestible to all malaria parasites

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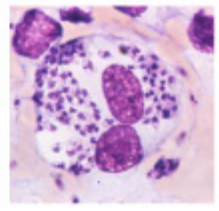
2.2.2 Other Blood and Tissue Protozoa

▼Table 6–2.2B Blood and Tissue Protozoa

Organism & Disease	Transmission	Pathogenesis	Key Vignette Clues	Diagnosis	Treatment
Hemoflagellates					
Trypanosoma brucei rhodesiense or *T. b. gambiense* (African sleeping sickness)	Saliva from tsetse bite	Localized inflammation at site of bite (Winterbottom sign) followed by parasitemia; organisms localize in blood vessels of heart and CNS; antigenic variation and polyclonal B cell activation cause vasculitis	Patient from Africa with fever, lymphadenopathy, rash, headache, and impaired mentation	Trypomastigotes in blood or CSF	• Blood stage: suramin • CNS: melarsoprol
T. cruzi (Chagas disease, American trypanosomiasis	Feces of reduviid (kissing) bug	Parasite invades when feces of bug are rubbed into wound or eyes after feeding (Romaña sign); parasitemia causes amastigote infection in cardiac and smooth muscle, megaesophagus, megacolon, cardiac failure	Patient from South America with dilated cardiomyopathy, achalasia	Trypomastigotes in blood	Nifurtimox or benznidazole
Leishmania donovani (visceral leishmaniasis, kala azar)	Sandfly bite	Amastigotes are intracellular in macrophages throughout the reticuloendothelial system	Patient from Africa, Middle East, or Asia with hepatosplenomegaly	Bone marrow, liver, spleen biopsy with amastigotes packed into macrophages	Stibogluconate sodium
L. tropica, L. major, and L. mexicana (cutaneous leishmaniasis)	Sandfly bite	Amastigotes are intracellular in macrophages of the skin	Patient with erosive skin lesions from Central or South America (*L. mexicana*) or Middle East (*L. tropica* and *L. major*)	Leishmanin skin test positive, amastigotes in biopsy materials 	Stibogluconate sodium
L. braziliensis (mucocutaneous leishmaniasis)	Sandfly bite	Amastigotes are intracellular in mucocutaneous macrophages	Patient from South America with disfiguring mucocutaneous lesions	Leishmanin skin test positive, amastigotes in biopsy materials	Stibogluconate sodium

From left to right: 1. Pascal Goetcheluck/Science Source; 2. Mary Ruebush; 3. Dr. James L. Castner/Visuals Unlimited, Inc. 4. Alliance Images/Alamy; 5. Sinclair Stammers/Science Source

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▼Table 6–2.2B Blood and Tissue Protozoa *(continued)*

Organism & Disease	Transmission	Pathogenesis	Key Vignette Clues	Diagnosis	Treatment
Miscellaneous apicomplexa					
Toxoplasma gondii (toxoplasmosis)	Oral from cat feces (cat is definitive host), No. 1 source in US: undercooked pork	Obligate intracellular organism replicates throughout the body, causing death of involved host cells; spread via the blood is possible in the tachyzoite stage, as is transplacental transmission; slow-growing cystic stages (bradyzoites) persist for life and may cause reactivational disease	Adult: flu-like; congenital; abortion, neonatal blindness, hydrocephalus, and neuropathies; AIDS: No. 1 cause of ring-enhancing lesions in CNS and No. 1 diagnosis at autopsy	Serology	Sulfadiazine, pyrimethamine
Babesia microti (babesiosis)	*Ixodes* tick bite	Intraerythrocytic trophozoites cause RBC lysis and anemia	Geographic range same as Lyme disease, summer months, patient has been outside, fever, anemia	Blood film reveals delicate intraerythrocytic ring forms, splenectomy predisposes, tetrads may be mentioned	Clindamycin and quinine
Free-living amebae					
Naegleria spp. (primary amebic meningoencephalitis–PAM)	Diving in warm freshwater	Amebae are forced through the cribriform plate; cause severe purulent, hemorrhagic inflammation extending from the olfactory bulbs to the rest of the brain	Summer months, child playing in recreational lakes, prefrontal headache, altered sense of smell, fever, death	Motile trophozoites in CSF	Amphotericin B plus rifampin (rarely successful)
Acanthamoeba spp. (granulomatous amebic encephalitis–GAE)	Through breaks in skin or mucous membranes, from soil or contaminated contact lens solution	Keratitis or hematogenous spread to cause diffuse necrotizing granulomatous encephalitis, insidious onset but progresses to death	No history of swimming; older individual or immunocompromised patient	Star-shaped cysts on biopsy	• Keratitis: miconazole • GAE: ketoconazole, sulfamethazine (rarely successful)

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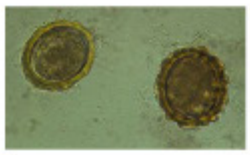
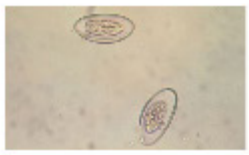
3 Helminth Parasites

3.1 Nematodes

▼ **Table 6–3.1** Nematodes

Organism	Pathogenesis	Clinical Findings	Diagnosis	Treatment
Transmitted by fecal-oral ingestion of ova				
Ascaris lumbricoides (large roundworm) 	Ova hatch in small intestine; larvae are carried to lung, coughed up, and swallowed; adult 30–40 cm in small intestine	Heavy infections: adults may block intestine, migrate extra-intestinally. Lung migration: verminous pneumonia, eosinophilia	Fecal exam; eggs are large, rough-shelled, and round to oval; sputum exam may reveal larvae, eosinophilia	Mebendazole
Trichuris trichiura (whipworm)	Larvae invade wall of cecum and colon, emerge as adults; damage to muscularis level	Diarrhea, abdominal pain, rectal prolapse	Fecal exam for eggs with bipolar plugs	Mebendazole
Enterobius vermicularis (pinworm) 	Female migrates out of anus at night and explodes; eggs on perianal skin cause itching	Child with severe perianal itching	Scotch-tape test; eggs are flattened on one side and contain infectious larvae	Mebendazole (treat all family members, daycare, and school contacts)
Visceral larva migrans (most commonly *Toxocara* canis; dog roundworm)	Larvae of dog roundworms, which *cannot* mature in humans, migrate aimlessly until they are killed by human immune response	Larvae may invade any tissue and induce necrosis, eosinophilic granulomas, and fibrosis	• Serology • Eosinophilia	• May be self-limiting • Corticosteroids in severe cases • Mebendazole • Keep pets wormed

1. Lauritz Jensen/Visuals Unlimited, Inc.; 2. John Durham/Science Source; 3. Carolina Biological Supply Co./Visuals Unlimited, Inc.; 4. Educational Images LTD/Custom Medical Stock Photo; 5. Educational Images LTD/Custom Medical Stock Photo

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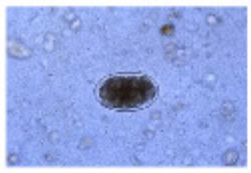
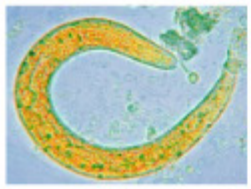
▼Table 6–3.1 Nematodes *(continued)*

Organism	Pathogenesis	Clinical Findings	Diagnosis	Treatment
Transmitted by skin penetration or ingestion of larvae				
Necator americanus (New World hookworm) and *Ancylostoma duodenale* (Old World hookworm) 	Larvae penetrate skin, migrate through lung, coughed up and swallowed, mature in small intestine, suck blood	Itching at site of skin penetration, rash, occasional cough with bloody sputum, diarrhea, abdominal pain and weight loss, iron deficiency anemia	Fecal exam for eggs, which are oval, clear-shelled, and golden brown, eosinophilia	Mebendazole
Strongyloides stercoralis (threadworm)	Larvae penetrate skin, migrate through lung, coughed up, and swallowed, mature in small intestine, and produce live larvae	Vomiting, diarrhea, anemia, and weight loss, occasional fatal cases caused by massive autoinfection, high rates in mental institutions	Fecal exam for larvae, eosinophilia	Thiabendazole
Trichinella spiralis 	Ingestion of larvae in meat (No. 1 source in U.S. is wild game); adults produced in small intestine immediately produce live larvae, which are carried via the blood to all striated muscles, where they encyst	Classical tetrad: fever, myalgia, splinter hemorrhages, eosinophilia, periorbital edema	Serologic tests, muscle biopsy, increased levels of muscle enzymes circulating in blood, eosinophilia	Mebendazole, corticosteroids
Cutaneous Larva Migrans (Commonly *Ancylostoma braziliense*; cat hookworm)	Larvae of dog and cat hookworms penetrate skin and wander until they are killed by the host immune response	Creeping eruption, plumber's itch, raised, pruritic, serpiginous skin rash on areas of skin exposed to soil	Clinical	Thiabendazole, topical corticosteroids

1. Science Source; 2. Educational Images LTD/Custom Medical Stock Photo; 3. Gary D. Gaugler/Science Source; 4. Carolina Biological Supply Co./Visuals Unlimited, Inc.; 5. Charles Stratton/Visuals Unlimited, Inc.

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▼ **Table 6–3.1 Nematodes** *(continued)*

Organism	Pathogenesis	Clinical Findings	Diagnosis	Treatment
Filarial nematodes				
Onchocerca volvulus (river blindness)	Blackfly (*Simulium*) transmits larvae, which mature to adulthood in subcutaneous nodules; adults produce microfilariae, which cause chronic inflammation in tissues	Allergic reaction to microfilariae migrating through the dermis leads to pruritic rash with darkened pigmentation; microfilariae in eyes can lead to blindness	Central and South America, West Africa; skin biopsy reveals microfilariae	Ivermectin: kills microfilariae, surgical excision of adult worms from nodules
Loa loa (African eye worm)	Deerfly (*Chrysops*) injects larvae, adults wander in subcutaneous tissues, cause allergic inflammation	Intense tearing, pain, disruption of vision	West Africa; recover adult worm from eye	Diethylcarbamazine
Wuchereria bancrofti and *Brugia malayi* (lymphatic filaria)	*Anopheles, Culex* or *Mansonia* mosquitoes transmit larvae, adults form in lymphatics, cause obstruction, granuloma formation, fibrosis	Low-grade fever, lymphadenitis, eosinophilia, leading to eventual elephantiasis	Blood examination for microfilariae, patient from Asia and South Pacific (*Brugia*) or Africa, Latin America, South Pacific Islands (*Wuchereria*)	Diethylcarbamazine
Dracunculus medinensis (Guinea worm)	Infection begins with ingestion of infected copepods in water, female migrates to skin to discharge larvae	Allergic symptoms occur during the release of larvae: nausea, vomiting, hives, and breathlessness	Adult worm erupts from skin, eosinophilia, increased IgE	Careful excision

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3.2 Cestodes (Tapeworms)

▼ **Table 6–3.2** Cestodes

Organism	Transmission	Symptoms	Diagnosis	Treatment
Taenia saginata (beef tapeworm)	Ingestion of cysticerci in beef	Asymptomatic or vague abdominal pain	Proglottids or eggs in stool	Praziquantel
Taenia solium (pork tapeworm)	Ingestion of cysticerci in pork	Asymptomatic or vague abdominal pain	Proglottids or eggs in stool	Praziquantel
	Cysticercosis, fecal-oral or autoinfection with eggs	Neurocysticercosis: ocular and neurologic problems, *adult-onset epilepsy*	Patient from endemic area (South America, Africa, Asia), imaging, larvae may calcify	Praziquantel, surgery
Diphyllothrium latum (fish tapeworm)	Ingestion of sparganum larva from poorly cooked fish	Abdominal pain, loss of weight, anorexia, malnutrition, and *B12 deficiency* problems	Patient from Great Lakes region, Northern Europe, Scandinavia, proglottids or eggs in stool	Praziquantel
Echinococcus granulosus	Fecal-oral contamination of ova from canines (definitive host)	Man becomes accidental intermediate host, hydatid cysts produce symptoms depending on location	Patient who has dogs that are used for herding, imaging, serology	Surgery, albendazole
E. multilocularis	Fecal-oral contamination of ova from wild canines (foxes, definitive host)	Man becomes accidental intermediate host, multilocular cysts produce symptoms depending on location	Imaging, serology	Surgery, albendazole

1. Carolina Biological Supply Co./Visuals Unlimited, Inc.; 2. SPL/Science Source; 3. Eric Grave/Science Source

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3.3 Trematodes (Flukes)

▼ **Table 6–3.3** Trematodes

Organism	Transmission	Symptoms	Diagnosis	Treatment
S. mansoni, *S. japonicum* (blood flukes)	Skin penetration by cercariae	Dermatitis, abdominal pain, bloody stool, chronic damage to liver by eggs results in cirrhosis	Patient from Africa or Asia, eggs in stool: • *S. mansoni:* large lateral spine • *S. japonicum:* small lateral hook	Praziquantel
Schistosoma haematobium (bladder flukes)	Skin penetration by cercariae	Dermatitis, hematuria and squamous cell bladder carcinoma	Patient from Egypt or Iraq, eggs in urine, large terminal spine	Praziquantel
Paragonimus westermani (oriental lung fluke)	Ingestion of larvae in raw crabs or crayfish	Similar to tuberculosis	Patient from Asia or South America, sputum examination for operculated eggs	Praziquantel
Fasciola hepatica (sheep liver fluke)	Ingestion of metacercariae on water plants	Subclinical to fever and malaise	Patient from Bolivia or Peru (not U.S.), fecal exam for operculated eggs	Praziquantel
Fasciolopsis buski (giant intestinal fluke)	Metacercariae on water chestnut	Epigastric pain, nausea, diarrhea, edema, ascites	Patient from India, China, Southeast Asia, operculated eggs in stool	Praziquantel
Clonorchis sinensis (Chinese liver fluke)	Cysts in raw fish	Inflammation and deformation of bile duct, hepatitis, anemia, and edema, risk of cholangiocarcinoma	Patient from Asia, operculated eggs in stool	Praziquantel

1. E. R. Degginger/Science Source

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Review Questions Chapters 5–6

1. A 16-year-old male presents to his physician with several weeks of slowly worsening pruritus of both of his feet, with erythematous, dry scaling lesions that are most obvious in the interdigital web spaces. Which of the following is most likely to be found on a potassium hydroxide (KOH) mount of a scraping of the affected skin?

A. Branching hyphae with rosettes of conidia
B. Budding yeasts
C. Cigar-shaped yeasts
D. Dichotomously branching, colorless septate hyphae
E. Hyphae with arthroconidia

2. Physical exam on an otherwise healthy man presents with several subcutaneous nodules on his hand. Examination of the exudate from one of the erythematous fluctuant lesions reveals cigar-shaped yeasts. What is the mechanism of action of the drug of choice for this infection?

A. Blockage of conversion of squalene into lanosterol
B. Blockage of formation of pyrimidines from precursors
C. Disruption of formation of microtubules
D. Inhibition of synthesis of ergosterol from lanosterol
E. Production of artificial pores in cytoplasmic membrane

3. A 54-year-old poultry farmer in rural Missouri presents to his physician with chronic cough, fever, and malaise. Chest radiograph reveals small calcifying pulmonary lesions and hilar lymphadenopathy. Which of the following is most likely to be found on biopsy of the lung?

A. Budding encapsulated yeasts
B. Curved septate hyphae with nests of yeasts
C. Double-walled spherules with endospores
D. Septate hyphae branching at acute angles
E. Yeasts packed inside alveolar macrophages

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Chapters 5–6 Review Questions

4. A male is admitted to hospital because of fever, chills, night sweats, and weight loss over the past few weeks. He has a tender, raised erythematous papule on the bridge of the nose. An x-ray shows consolidation of the right middle lobe of the lung, but a PPD skin test is negative. A bronchoscopy is performed and a silver-stained specimen shows large, round budding yeasts with broad bases connecting the mother cell to the daughter cell. Which of the following is the correct pairing of causal agent and infectious form in this case?

	Causal Agent	Infectious Form
A.	*Blastomyces dermatitidis*	Septate hyphae with oval conidia
B.	*Candida albicans*	Yeasts and pseudohyphae
C.	*Coccidioides immitis*	Arthroconidia and hyphae
D.	*Cryptococcus neoformans*	Encapsulated yeasts
E.	*Histoplasma capsulatum*	Tuberculate macroconidia and microconidia

5. A 27-year-old male presents with fever, night sweats, cough, and weight loss. He has had multiple sex partners. His chest x-ray shows bilateral pulmonary infiltrates with interstitial and alveolar markings. His CD4 count is 125. Which of the following is the mechanism of action of the drug of choice for his pneumonia?

A. It blocks production of tetrahydrofolic acid
B. It blocks the activity of fatty acid synthase
C. It blocks the activity of the 50S ribosomal subunit
D. It blocks the conversion of lanosterol into ergosterol
E. It inhibits viral DNA polymerase

6. A 20-year-old man complains of cramping abdominal pain and diarrhea that is worse after meals for the past 3 weeks. He has lost 10 pounds in the same time period. His symptoms began 2 weeks after returning from a camping trip in upstate New York. His vital signs and physical exam show no abnormalities. Which of the following diagnostic tests would be most likely to identify the causal agent?

A. Culture the stool on eosin-methylene blue agar
B. Duodenal aspiration
C. Electron microscopy of the stool
D. EIA for toxin in stool
E. Proctoscopy and rectal biopsy

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Review Questions Chapters 5–6

7. A 31-year-old news correspondent on his return from Indonesia complains of tiredness, sore muscles, and spiking fevers. He subsequently develops a disabling illness complicated by severe anemia, pulmonary edema, renal failure, and shock. Which of the following is the correct pairing of means of infection and causal agent in this case?

	Means of Infection	Causal Agent
A.	Ingestion of metacercariae	*Clonorchis sinensis*
B.	Injection by mosquito	Yellow fever virus
C.	Injection by mosquito	Dengue virus
D.	Sporozoites injected by mosquito	*Plasmodium falciparum*
E.	Sporozoites injected by tick	*Babesia microti*

8. A middle-aged AIDS patient is brought into the emergency room after experiencing a seizure witnessed by several friends. The observers relate that the patient suddenly lost consciousness and his limbs began jerking. The man's tongue has been severely bitten, and loss of bowel and bladder control is evident on admission. On physical exam, the patient is lethargic, unable to answer simple questions, and has left-sided hemiparesis. An MRI of the head reveals multiple-ring enhancing lesions. Which of the following would most likely be found on a biopsy of one of these lesions?

A. Central liquefactive necrosis with intracellular tachyzoites proliferating outward
B. Neutrophils and bacteria
C. Pleomorphic astrocytes with marked atypia
D. Thin-walled, calcified cysts containing cysticercal larvae
E. Hemorrhage and liquefactive necrosis

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Chapters 5–6 Review Questions

9. A 31-year-old Hispanic woman is brought to the emergency room after suffering a seizure at home. The patient has been a resident of the United States for five years, but occasionally travels to her previous home in the Dominican Republic. CT scan of the head reveals multiple punctate calcifications, and two enhancing cystic lesions with surrounding edema. Which of the following is the most direct source of her cerebral lesions?

A. Autoinfection
B. Exposure to swine feces
C. Exposure to cat feces
D. Ingestion of poorly cooked pork
E. Unsafe sexual practices

10. A child is brought to the pediatrician because of perianal itching. Physical examination reveals scaly skin in the perianal region. A scotch-tape test reveals oval eggs that are flattened on one side. What is the mechanism of action of the drug of choice in this case?

A. It blocks enzymes involved in arachidonic acid metabolism
B. It causes degeneration of microtubules and blocks glucose uptake
C. It increases the opening of glutamate-gated chloride channels
D. It is an agonist at nicotinic acetylcholine receptors
E. It is an organophosphorus cholinesterase antagonist

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Review Answers Chapters 5–6

1. The correct answer is E. This patient has athlete's foot or tinea pedis, caused by any of a number of dermatophytic fungi in the genera *Trichophyton, Epidermophyton*, and *Microsporum*. The infection is diagnosed by the finding of hyphae and arthroconidia in KOH-treated scrapings of the affected area.

2. The correct answer is D. The patient has sporotrichosis, or rose gardener's disease. It is treated with itraconazole, and the mechanism of action of this drug is to inhibit the conversion of lanosterol into ergosterol, the fungal essential membrane sterol. Amphotericin D may also be used, but has high toxicity. It acts by producing artificial pores in the fungal cell membrane.

3. The correct answer is E. The patient has histoplasmosis, caused by *Histoplasma capsulatum,* which is found in virtually 100% of the chicken roosts in the endemic area. It is diagnosed by the finding of small intracellular yeasts packed with macrophages in the lung.

4. The correct answer is A. The patient has blastomycosis, which is caused by the dimorphic fungus, *Blastomyces dermatitidis*. It is acquired from inhalation of septate hyphae with conidia from rotting wood and is found in the Mississippi and Missouri river beds and along the East Coast of the U.S.

5. The correct answer is A. The patient is most likely infected with *Pneumocystis jirovecii*, which typically onsets in AIDS patients when the CD4 cell count falls below 200. The drug of choice is trimethoprim-sulfamethoxazole which is a synergistic combination of a sulfonamide and a dihydrofolate reductase inhibitor. Together they inhibit production of tetrahydrofolic acid.

6. The correct answer is B. The patient most likely is suffering from giardiasis, caused by *Giardia lamblia*. This protozoan parasite lives in the upper small intestine and blocks the small bile ducts entering the area. Although it is shed into the stool irregularly, the most reliable method of finding the trophozoites is by duodenal aspiration.

7. The correct answer is D. The travel history, severity of fever, anemia, and complications indicate that the patient is most likely infected with *Plasmodium falciparum* malaria. The infection is transmitted by the bite of the female *Anopheles* mosquito, which injects sporozoites into the host with her anticoagulant saliva.

8. The correct answer is A. The most likely cause of ring-enhancing lesions in the brain of an AIDS patient is reactivational disease due to *Toxoplasma gondii*. The rapidly dividing intracellular forms (tachyzoites) will be found spreading out from a central point of necrosis.

9. The correct answer is A. The patient most likely has neurocysticercosis, which occurs when a patient with adult *Taenia solium* tapeworms in the intestine accidentally transmits eggs of the worms to the mouth and subsequently develops larval forms called cysticerci throughout the body. Infection of humans with adult *Taenia solium* is acquired from ingesting poorly cooked infected pork, but cysticercosis is acquired by autoinfection.

10. The correct answer is B. The child has pinworm, or *Enterobius vermicularis* infection. The drug of choice for most nematode infections is mebendazole, which acts by disrupting microtubule function and therefore blocking glucose uptake.

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Taxonomic Charts

Abbreviations Used

→	means progressing on to
~	means about or approximately
↑	increasing
↓	decreasing
abd	abdominal
AIDS	acquired immunodeficiency syndrome (CD4+ count <200)
attntd	attenuated
CA	cancer
CF	cystic fibrosis
CGD	chronic granulomatous disease
CMI	cell-mediated immunity
CNS	central nervous system
CVS	cardiovascular system
CYS	cysteine
DOC	drug of choice
Drha	diarrhea
dx	diagnosis
EV	encephalitis virus
Fac	facultative
Fac IC	facultative intracellular
FQ	fluoroquinolones
FTA-Abs	Fluorescent Treponemal Antibody Absorption
GU	genitourinary
HIV+	patient with known human immunodeficiency virus infection; can be used for anyone who is infected but often used for those who are HIV+ but do not have AIDS (in other words, CD4+ count >200)
IC	immunocompromised
Infl'd	inflamed
Infl'n	inflammation
infxn	infection
IUD	intrauterine device
IV	intravenous
LOS	lipooligosaccharide
mo	month(s)
NF	normal flora
obl. IC	obligate intracellular
occ	occasional
ox phos	oxidative phosphorylation
PMNs	polymorphonuclear leukocytes
pt	patient
®	resistant
RBCs	red blood cells
recrnt	recurrent
RPR	rapid plasma reagin
RSV	respiratory syncytial virus
Rx	treatment
Ⓢ	sensitive
subQ	subcutaneous
URT	upper respiratory tract
UTI	urinary tract infection
VDRL	Venereal Disease Research Lab
WNV	West Nile Virus
xrxn	cross-reaction

If there are multiple causal agents, at the end of the description there may be a # with the abbreviation "CA." This means you should be able to list that number. If it specifically says "species," you should give species.

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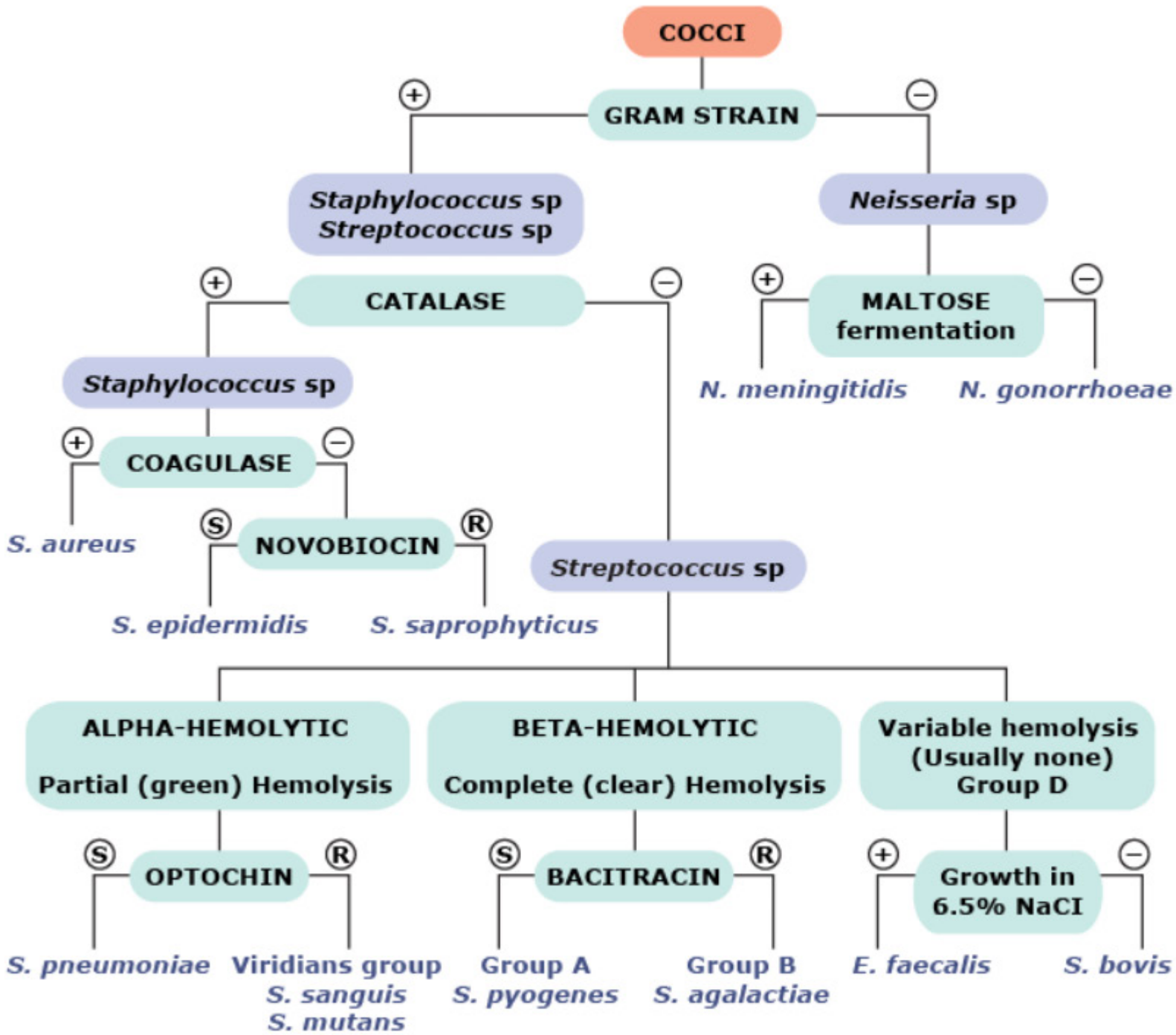

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COCCI

Gram ⊕

Staphylococcus sp

Coagulase ⊕
S. aureus
- NF in nose, skin
- Protein A
- β-hemolytic
- Heat-stable enterotoxins
- CAMP test hemolysin
- Salt-tolerant
- Mannitol salt agar
- Yellow/gold pigment
- Toxic Shock synd
- Scalded Skin synd
- Abscesses
- Food poisoning (2-6 h)
- Acute endocarditis in IV drug users
- Acute osteomyelitis
- DOC: MSSA: Nafcillin
- MRSA: Vancomycin
- VRSA: Quinupristin

Coagulase ⊖
S. epidermidis
- Non-hemolytic
- Biofilm
- NF in skin, nose, mouth, gut
- Subacute endocarditis in IV drug users
- Catheter, prosthetic device infections
- Novobiocin sensitive

Coagulase ⊖
S. saprophyticus
- Non-hemolytic
- UTI in sexually active adolescents
- Novobiocin resistant

Gram ⊖

Neisseria sp
- Kidney-bean-shaped diplococci
- Catalase (+)
- Oxidase (+)
- IgA protease
- Overproduces LOS
- Oxidizes glucose
- Chocolate agar
- Candle jar, CO_2

Oxidizes maltose
N. meningitidis
- Polysaccharide capsule
- β-Lactamase (rare)
- Pili
- Colonizes URT
- Waterhouse-Friderichsen synd.
- Tetravalent vaccine (Y, W-135, C, A)
- DOC: Cefotaxime, ceftriaxone

Does not oxidize maltose
N. gonorrhoeae
- No capsule
- β-Lactamase
- Pili
- Thayer-Martin medium
- DOC: Ceftriaxone PLUS Tetracycline for *Chlamydia*
- No vaccine

Also
- *Moraxella*
- *Veillonella*
- *Elkenella*
- *Kingella*

Gram ⊕

Streptococcus sp

Alpha Hemolytic

S. pneumoniae
- Lancet-shaped
- Capsule
- Quellung (+)
- IgA protease
- Optochin sensitive
- Lysed by bile
- NF in URT
- #1 for pneumonia >60 yr
- #1 for adult meningitis
- #1 Otitis media in kids
- DOC: Macrolides, ceftriaxone, amoxicillin
- ~20% Pen resist.
- Vaccine for elderly (23 serotypes)
- Vaccine pediatric (13 serotypes conjugated to protein)

Viridans group
S. sanguis
S. mutans
- NF oropharynx
- Dextran biofilm, dental caries
- Subacute endocarditis (post-dental work or poor dental hygiene)
- DOC: Penicillin + aminoglycosides

Beta Hemolytic

Group A
S. pyogenes
- Capsule-hyaluronic acid
- M protein
- Streptolysin O
- Streptolysin S
- Streptokinase
- Hyaluronidase
- Erythrogenic toxin (SPE-A)
- Rheumatic fever
- Post-Strep acute GN
- Cellulitis
- Impetigo
- DOC: Penicillin G/V

Group B
S. agalactiae
- CAMP Test (+) (incomplete hemolysin)
- Hydrolyzes hippurate
- Colonizes vagina in 15-20%
- Screen preg, treat with ampicillin ↓ meningitis
- #1 for neonatal meningitis (↓ing)
- DOC: Ampicillin + aminoglycoside

Variable Hemolytic

Group D
E. faecalis
- Enterococcus
- Hydrolyzes bile esculin with black complex
- Salt-tolerant
- NF in colon, gut
- UTI
- Bilary tract infections
- Subacute endocarditis post surgical or assoc. of colon cancer
- Opportunistic infxns
- DOC: Sensitivity testing

Group D
S. bovis
- Non-enterococcal
- Hydrolyzes bile esculin with black complex

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GRAM (+) RODS

SPORE-FORMING

Aerobic

Motile

B. cereus
- Heat-stable exotoxin: Vomiting increase cAMP
- Heat-labile toxin: Diarrhea
- Fried rice
- Food poisoning (2-18 h)
- Symptomatic Rx

Non-Motile

B. anthracis
- Poly-D-glutamate capsule
- In R-E cells
- Toxin: Protective Ag, lethal factor, edema factor (an adenylate cyclase)
- Painless skin ulcer 95%
- Black eschar
- Striking local edema
- Woolsorter's disease Pneumonia
- DOC: Ciprofloxacin or doxycycline

Anaerobic

Motile

C. tetani
- Terminal spores
- Exotoxin: Tetanospasmin, inhibits GABA, glycine
- Tetanus Spastic paralysis
- DOC: Hyperimmune globulin, penicillin + Spasmolytic
- Toxoid vaccine

C. botulinum
- Neurotoxin heat-labile blocks ACh release
- Flaccid paralysis
- Canned-foods, vacuum-packed fish
- Trivalent antitoxin
- DOC: Antitoxin + Penicillin
- Infant botulism human hyperimmune, serum, no drugs

C. difficile
- Nosocomial
- Antibiotic (Clindamycin) usage
- Diarrhea → pseudomembranous colitis
- Yellow plaques
- Colon
- Toxins A + B
- DOC: Change or stop antibiotic

Non-Motile

C. perfringrens
- Subterminal spore
- Alpha lecithinase = Phospholipase C
- Enterotoxin
- Stormy fermentation
- Double-zone hemolysis
- Egg yolk agar
- Normal in colon
- Food poisoning
- Gas gangrene
- Myonecrosis
- High mortality
- DOC: Penicillin G ± Clindamycin PLUS debridement

NON-SPORE-FORMING

Aerobic

Motile

L. monocytogenes
- Tumbling motility
- "Jets" from cell to cell
- Fac IC
- β-hemolytic
- Cold enrichment
- Sepsis
- Crosses placenta
- Meningitis #1-Renal transplant Neonatal Cancer
- DOC: Ampicillin and Gentamicin for IC

Non-Motile

C. diphtheriae
- Club-shaped
- "Chinese Characters"
- Exotoxin (ADP-R of eEF-2) heart, nerves, epithelium
- Volutin granules on Loeffler's medium
- Tellurite: black colonies
- ELEK test
- Gray pseudomembrane
- Myocarditis
- Recrnt laryngl nerve palsy
- DOC: Antitoxin + Erythromycin
- Toxoid vaccine

N. asteroides
- Filaments to rods
- Urease (+)
- Partially acid-fast
- Cavitary bronchopulmonary
- Multiple brain abscesses
- Mycetoma (granules)
- DOC: Sulfonamides

Anaerobic

A. israelii
- Branching rods
- Non-motile
- "Sulfur" granules in exudates from sinus tract
- NF in mouth and female GU
- Invasive growth
- Cervicofacial (lumpy jaw)
- IUD-associated infections
- Solitary brain abscess
- Mycetoma
- Rx: Penicillin + drainage

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SPIROCHETES

- Gram negative anatomy, poorly staining
- Spiral-Shaped
- Axial Filaments (motile)
- Jarisch-Herxheimer Rxn

Treponema sp

- *T. pallidum*-Syphilis cannot be cultured
- 1°—PAINLESS chancre, infectious
- 2°—RASH, condylomata lata, infectious
- 3°—Gummas, CVS, CNS
- Congenital: Stillbirths, malformed
- VDRL & RPR—Screening tests
- Reagin ab—xrxn with cardiolipin
- FTA-ABS (specific test)
- Dark-field microscopy
- DOC: Benzathine penicillin

Borrelia sp

- Microaerophillic
- Giemsa stain
- *B. burgdorferi*
  Lyme disease
  (*I. scapularis*), *I. pacificus*
  Reservoirs: Mice, deer
  CT, WI, CA
  Erythema Migrans
  Target lesions
- *B. recurrentis*
  Relapsing fever
  Vector: Body louse
  Antigenic variation
- DOC: Penicillin or azithromycin

Leptospira sp

- Dark-field microscopy
- Contaminated water, animal urine
- Fever, jaundice, uremia
- Non-icteric Leptospirosis: Meningitis—No PMN in CSF, uveitis, rash
- Icteric Leptospirosis: Weil disease, renal failure, myocarditis
- DOC: Penicillin G or doxycycline

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GRAM (-) RODS

Facultative Anaerobes

AEROBES, Oxidase Positive

B. pertussis
- Adhesion via hemagglutinin and pertussis toxin
- Adenylate cyclase toxin (local edema)
- Tracheal toxin
- Dermanecrosis toxin
- Endotoxin
- Bordet-Gengou or Regan-Lowe agar
- Whooping cough
- DOC: Erythromycin
- Vaccine-toxoid + filamentous hemagglutinin

Brucella sp
- Fac IC
- Endotoxin
- Requires CYS, CO_2
- Unpasteurized milk
- Undulant fever
- *B. abortus* cattle: Mild
- *B. suis* pigs: Suppurative, chronic
- *B. melitensis* goats: Severe, acute
- DOC: Rifampin and doxycycline

Bartonella henselae
- Cat scratch fever
- Bacillary angiomatosis in AIDS

F. tularensis
- Fac IC
- Requires CYS
- *Dermacentor* tick bite Transovarian trans.
- Aerosol
- Rabbits, rodents
- Tularemia—AR, MO, TX
- Granulomatous
- DOC: Streptomycin
- Live, attntd vaccine

L. pneumophila
- Fac IC
- Requires CYS & Fe
- Buffered Charcoal Yeast agar
- Dieterie silver stain
- Water-loving, air conditioning
- Not contagious
- Atypical pneumonia
- Mental confusion
- Diarrhea
- DOC: Erythromycin

P. aeruginosa
- Slime-layer (capsule)
- Grape-like odor
- Exotoxin A: ADP-R of eEF-2 in liver
- Pigments pyocyanin, pyoverdin
- Transient colonization, in 10% of normal pop
- Osteomyelitis in drug abusers
- Pneumonia in cystic fibrosis
- Nosocomial infections, burn patients, neutropenic patients
- Ecthyma gangrenosum
- DOC: Penicillin + Aminoglycoside

Obligate ANAEROBES

Bacteroides spp.
- Modified LPS, capsule
- Predominant colonic flora
- Normal in oropharynx, vagina
- Predisposing factors: Surgery, trauma chronic disease (cancer)
- Septicemia, peritonitis, aspiration pneumonia
- *Prevotella melaninogenica:* Human oropharynx
- Fusobacterium (combined w/ *Treponema microdentium*): Vincent's angina, trench mouth
- DOC: Metronidazole

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GRAM NEGATIVE, FACULTATIVE ANAEROBIC OXIDASE POSITIVE, RODS

Pasteurella multocida

- Requires CYS
- Animal bites (cats & dogs)
- Cellulitis, lymphadenitis
- DOC: Amoxicillin/Clavulanate (prophylaxis)

Haemophilus influenzae

- Polyribitol capsule
- Quellung (+)
- IgA protease
- Requires X (Hemin), V (NAD)
- Normal in nasopharynx and conjunctiva
- Pathogenic in kids: Type B
- Meningitis in 1–2 yr
- Otitis media, pneumonia
- Acute epiglottitis
- DOC: Cefotaxime/Ceftriaxone
- Prev: HIB vaccine, rifampin
- *H. ducreyi:* Soft, painful genital chancroid

Vibrio sp

- Polar flagella, comma-shaped
- Enterotoxin (Choleragen) ADP-R, increases cAMP
- Catalase (+)
- Alkaline culture (TCBS)
- Classic cholera O_1
- Biotypes: El Tor, Cholerae
- Rice-water stools
- Severe dehydration
- Rx: Fluid & electrolytes tetracycline for contacts
- *V. parahaemolyticus:* Catalase (-), salt-tolerant, raw seafood
- *V. vulnificus:* Brackish-water oysters, cellulitis, septicemia DOC: Tetracycline

Campylobacter sp *Helicobacter* sp

- Microaerophillic
- Polar flagella
- Comma or S-shaped
- Catalase (+)
- Skirrow's agar CO_2
- Invasive
- *H. pylori:* 37°C, urease (+) gastritis, ulcers carcinoma
- DOC: Omeprazole + amoxicillin + clarithromycin
- *C. jejuni:* 42°C, No. 1 bacterial diarrhea U.S.A.
- "Gull Wings"
- DOC: Erythromycin, fluoroquinolones

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GRAM NEGATIVE, FACULTATIVE ANAEROBIC OXIDASE NEGATIVE RODS

ENTEROBACTERIACEAE

- Ferment Glucose
- Oxidase (-), Catalase (+)
- Reduce Nitrates to Nitrites

Lactose-Fermenting

Escherichia coli

- NF in colon
- #1 for UTI
  P-pili, X-Adhesins
- Nosocomial infections
- Neonatal meningitis (K1 capsule)
- ETEC—Traveler's diarrhea
  Toxins: LT, ST
- EIEC—Invasive
- EHEC—VTEC 0157:H7, hemorrhagic colitis, hemolytic uremic S, does not ferment sorbitol
- EPEC
  Plasmid-coded EAF
- EAEC
  Fimbriae/biofilm
- DAEC
  Infants
  Bacteria in microvilli
- DOC: Ampicillin or sulfonamides, cephalosporins

Klebsiella pneumoniae

- Capsule
- Quellung (+)
- Typical pneumonia in chronic lung disease, alcoholism, aspiration, currant jelly suptum
- UTI:
  Nosocomial, catheterization
- DOC: Cephalosporin +/- aminoglycoside

Non-Lactose-Fermenting

Motile and H_2S-Producing

Proteus sp.

- Swarming motility
- Indole (+), Urease (+)
- UTI, septicemia
- Staghorn calculi
- DOC: Fluoroquinolones

Salmonella enterica subsp.

- Antigens: Vi, O, H
- EMB/MacConkey
- Predisposing factors: High gastric pH, gastrectomy
- Widal test (O, H, Vi)
- Osteomyelitis in sickle cell disease
- *S. enterica* subsp. *typhi:* No animal res., no H_2S produced, invasive (R-E) cells, rose spots
- DOC: Fluoroquinolones or cephalosporins
- *S. enterica* subsp. *enteritidis:* Poultry, reptiles, Rx: Symptomatic
- DOC for invasive: Ampicillin, cephalosporins

Non-Motile and Non-H_2S-Producing

Shigella sp.

- No H Antigens
- Invasive
- Shigatoxin
  Nicks 60S
  Neurotoxin
  Cytotoxin
  Enterotoxin
- Enterocolitis
- Bloody diarrhea
- DOC: Fluid and electrolytes, FQ, azithromycin

Y. pestis

- Coagulase (+)
- V&W antigens
- Bipolar staining Wayson's stain
- Wild rodents
- Flea bite
- Southwest U.S. (Sylvatic)
- Bubonic plague fever, buboes, conjunctivitis
- Pneumonic plague
- Rx: Aminoglycosides + quarantine (72 h)
- *Y. enterocolitica:* Cold growth, heat-stable toxins, pseudoappendicitis

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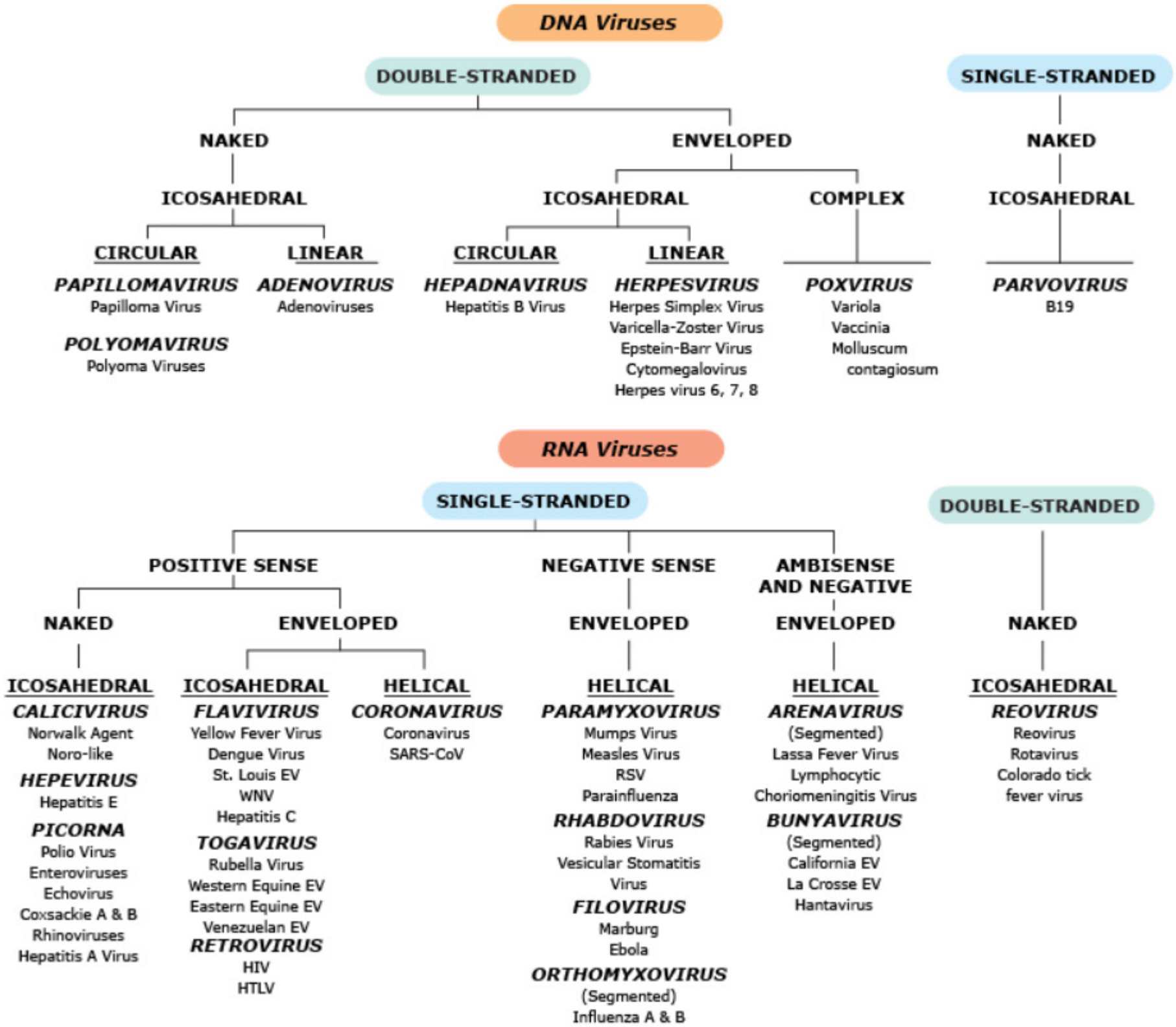

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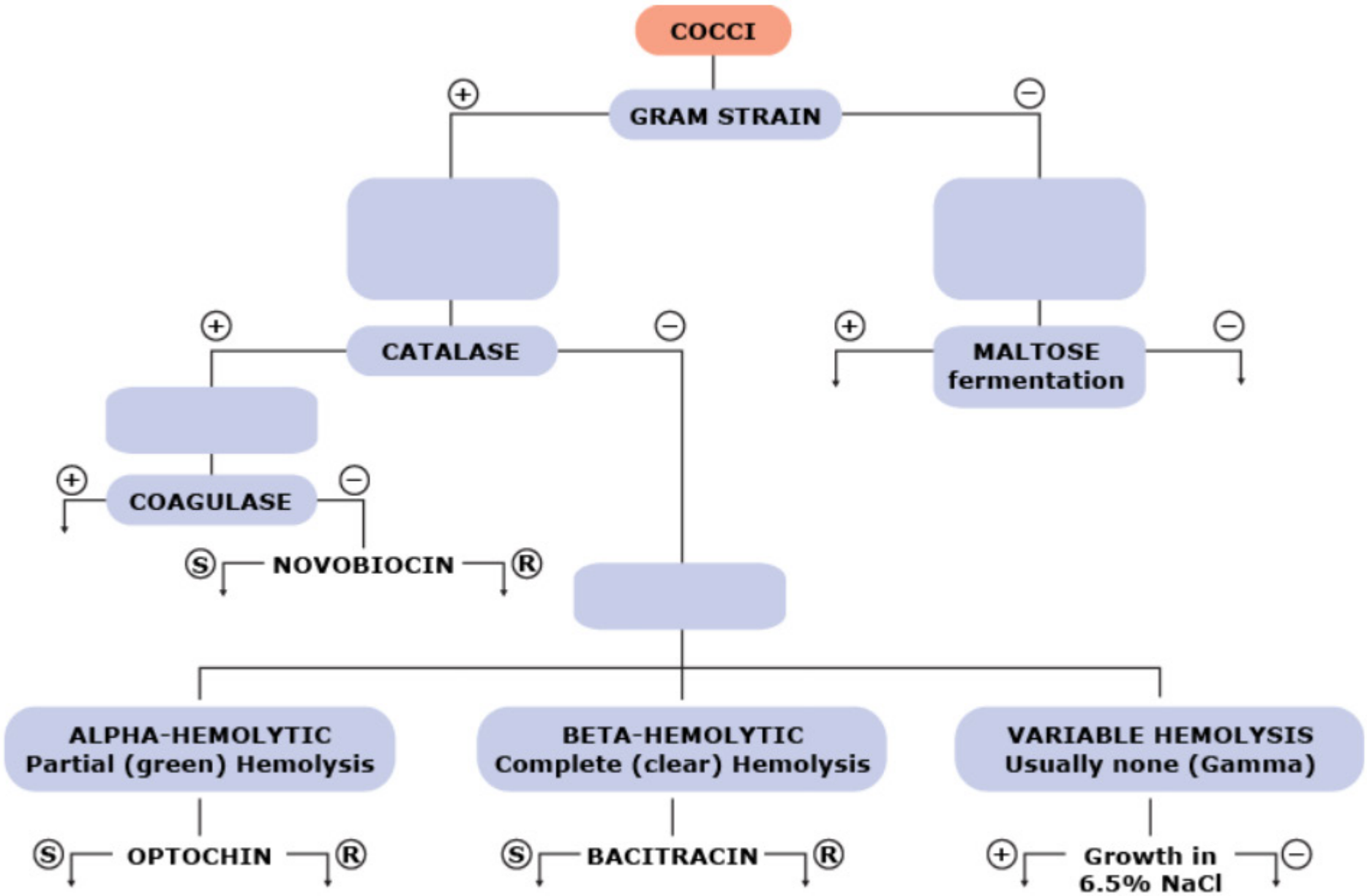

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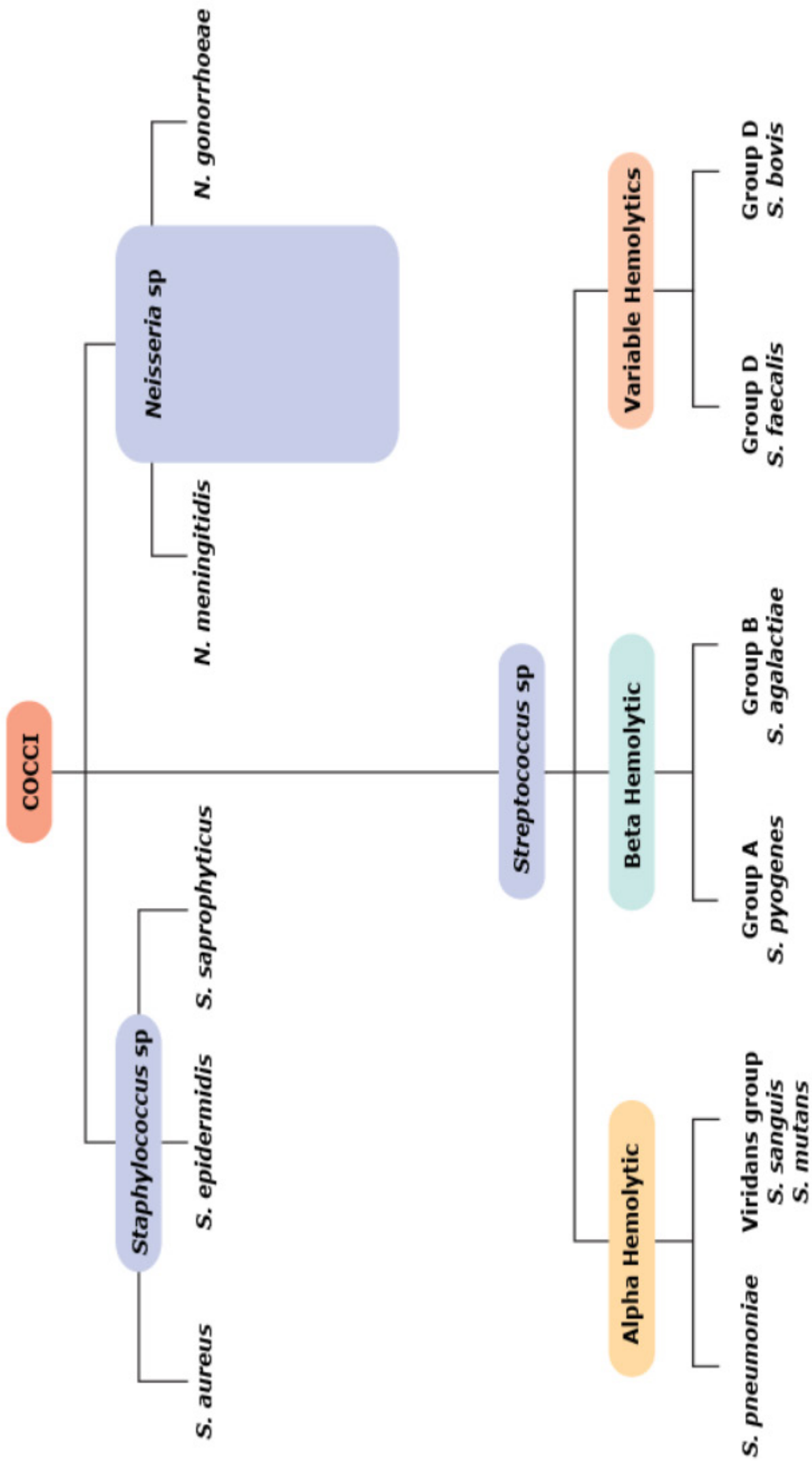

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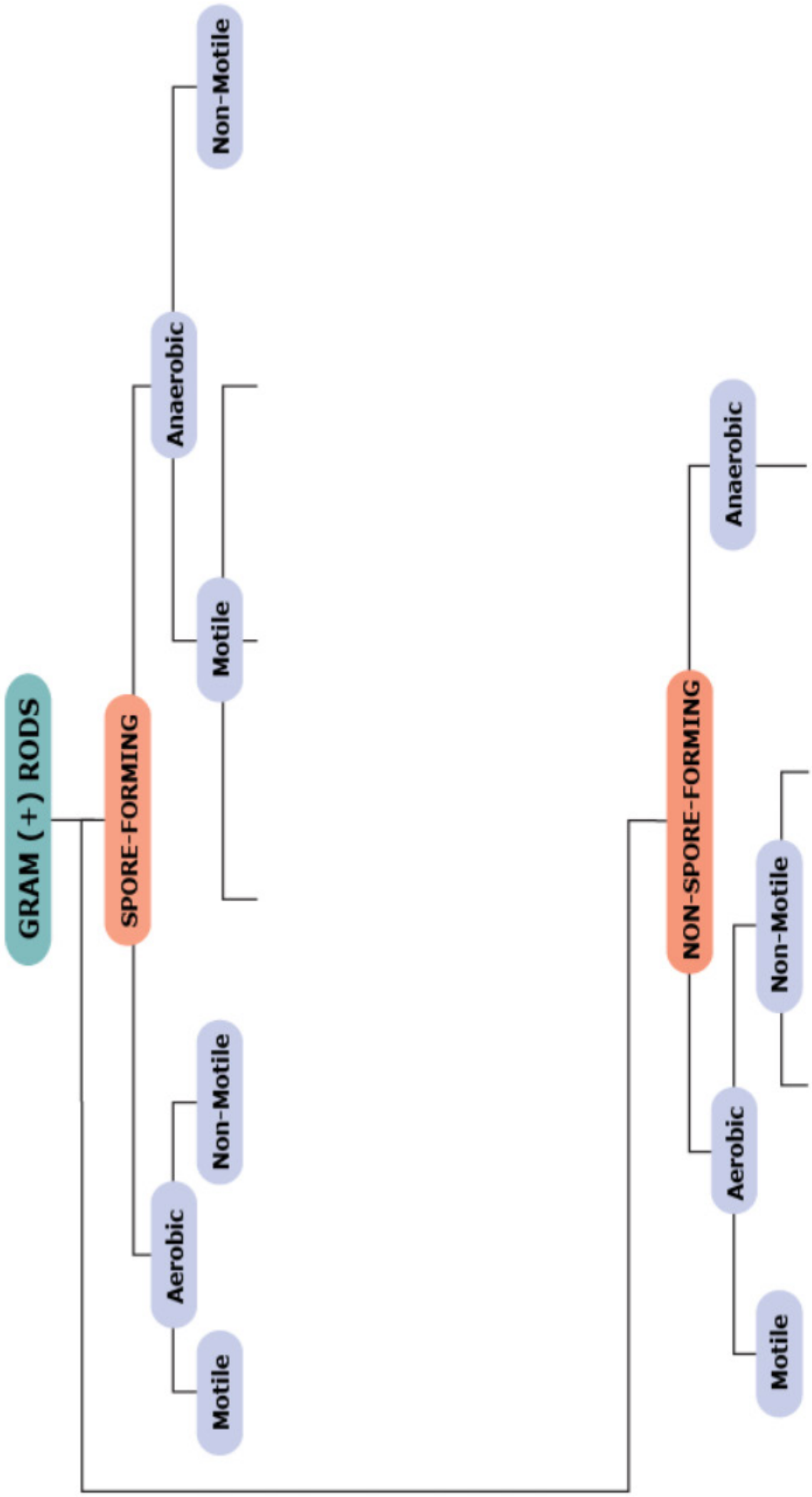

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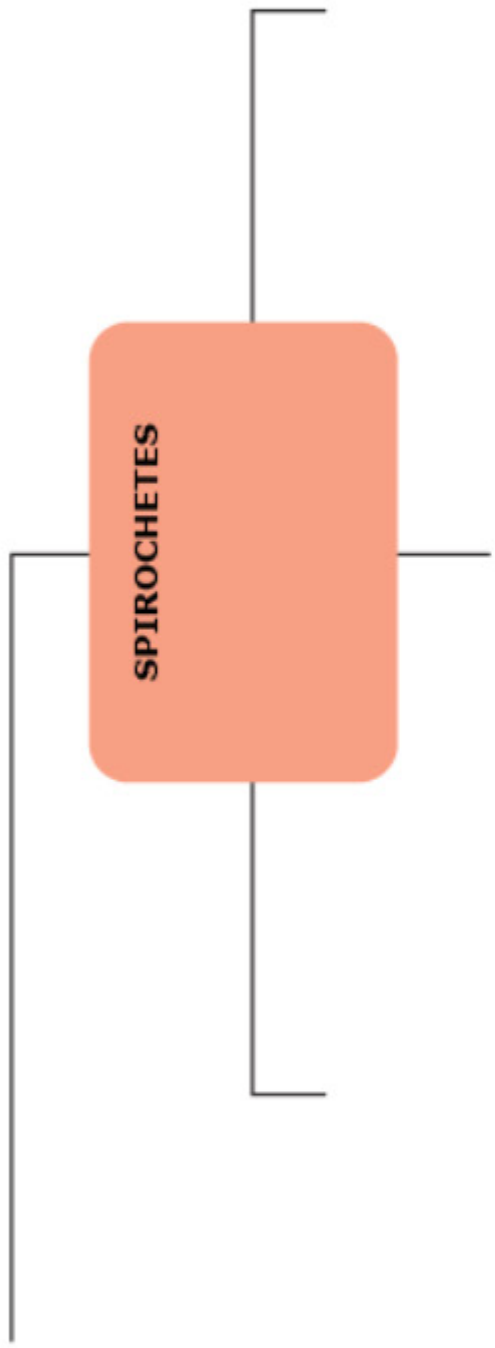

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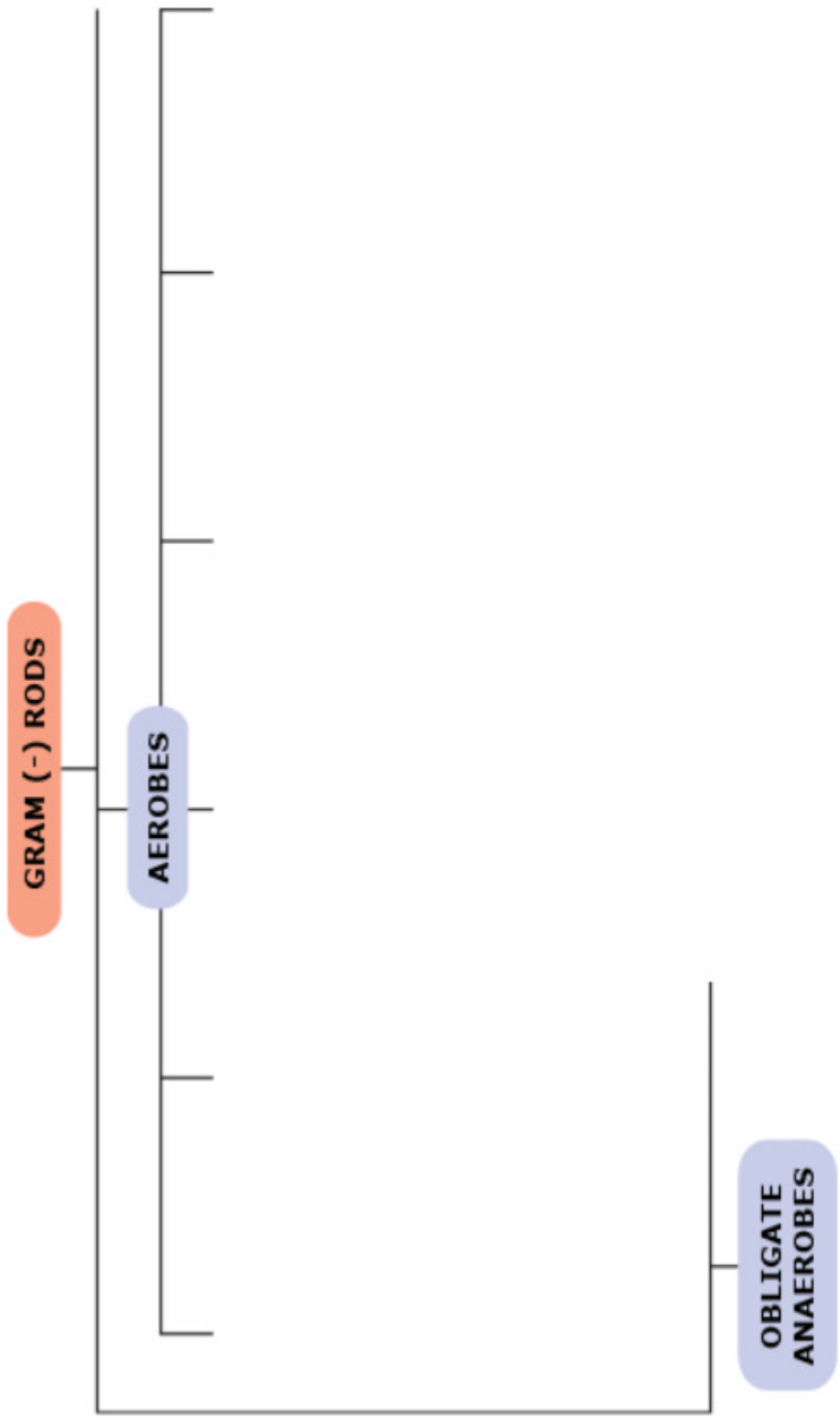

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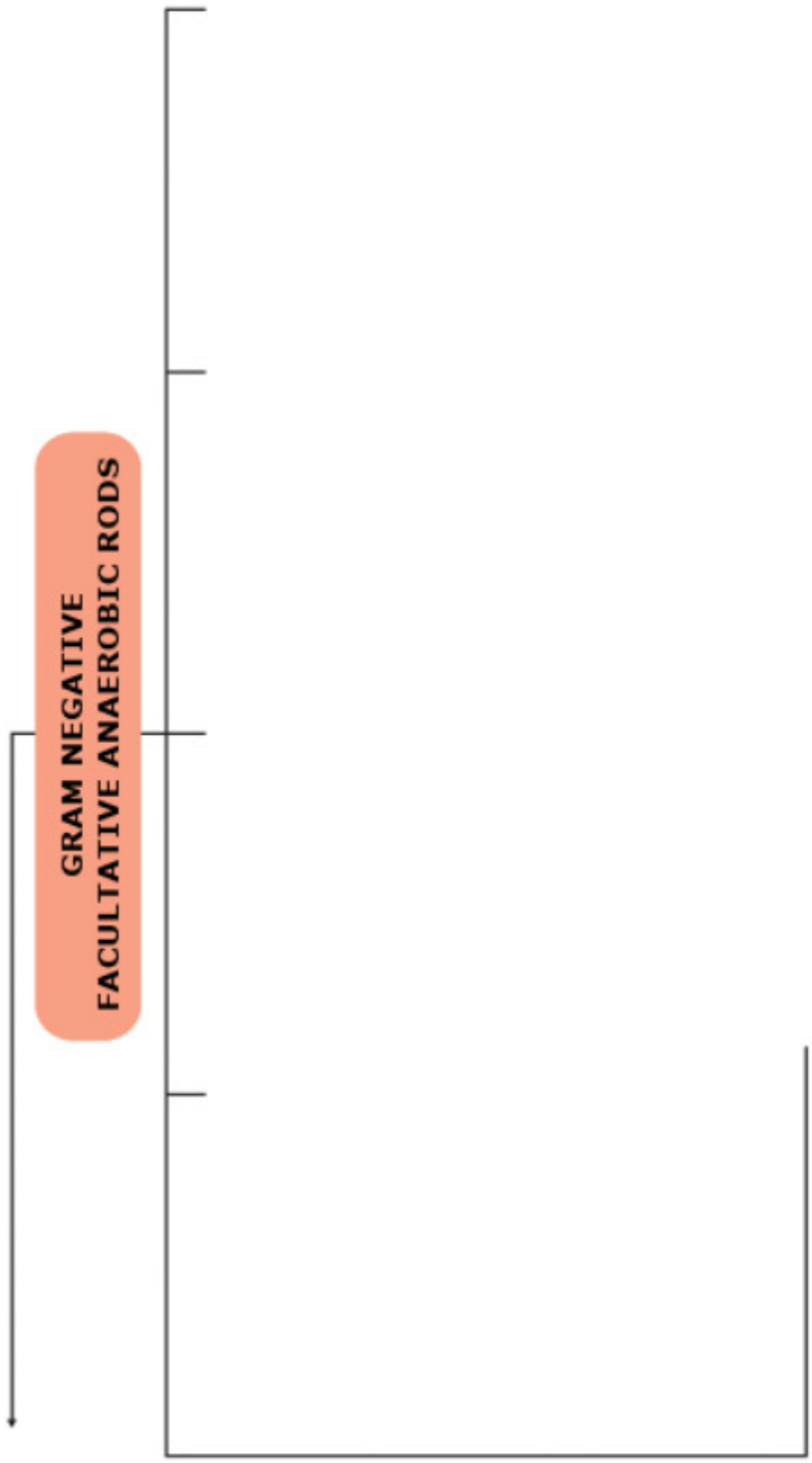

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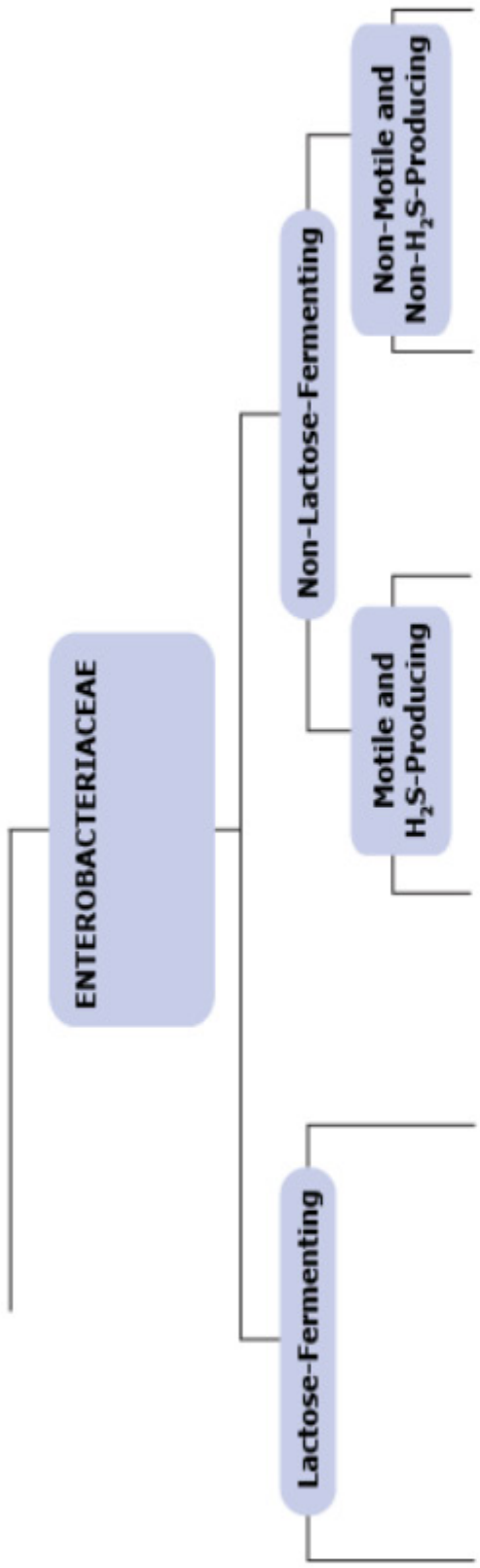

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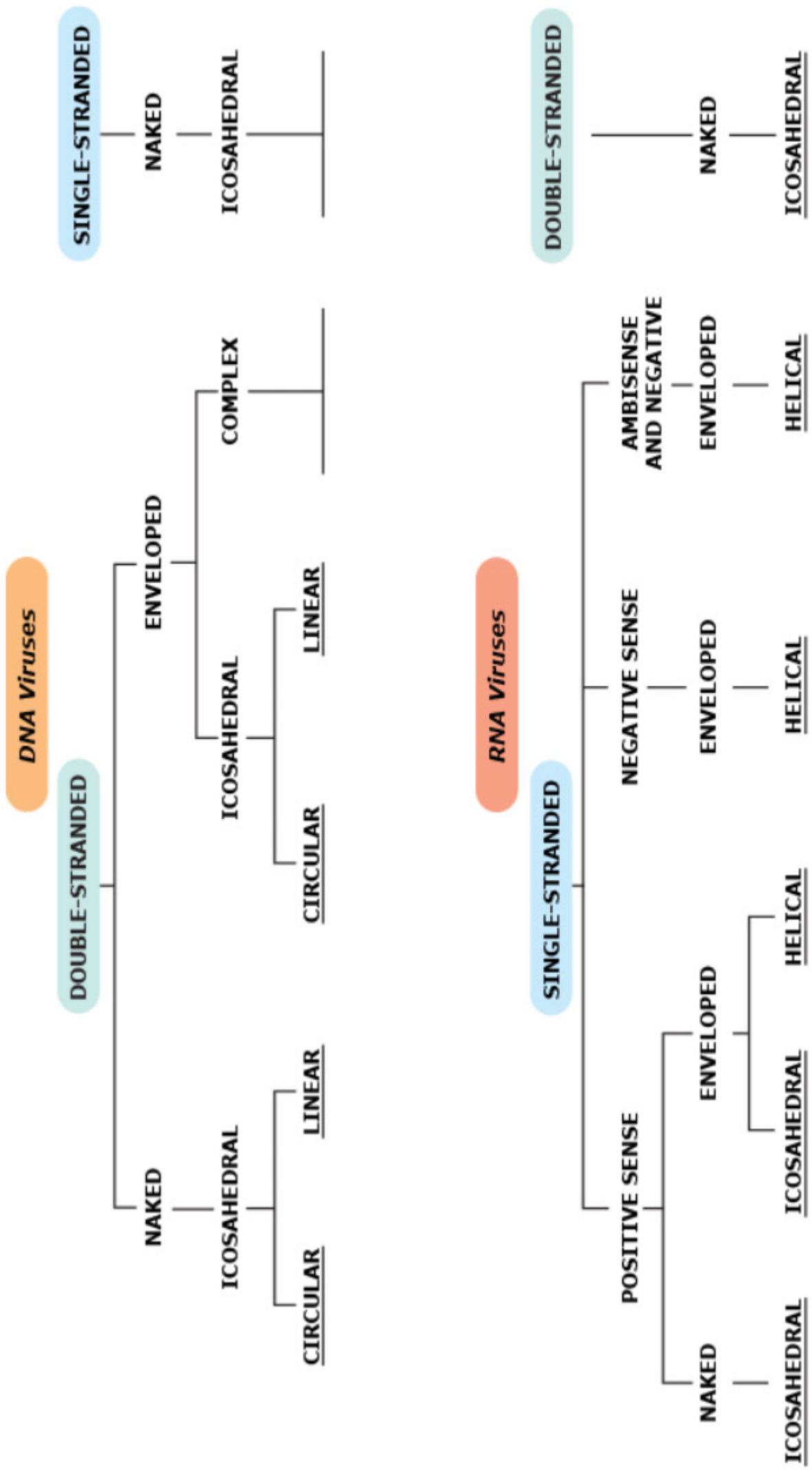

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Collected Concepts for Memorization

1 Anatomy and Physiology

▼**Table A-2.1A** Microbial Surface Structures

Function	Factor	Microbe
Attachment	**Biofilm**	• *Pseudomonas aeruginosa* • *Staphylococcus aureus* • *S. epidermidis* • Viridans Streptococci
	Lipoteichoic acids	All gram positives
	Pili	Most gram negatives
Anti-phagocytosis	**Capsules**	Primary: • ***S**treptococcus pneumoniae* • ***K**lebsiella pneumoniae* • ***H**aemophilus influenzae* • ***P**seudomonas aeruginosa* • ***N**eisseria meningitidis* • ***S**almonella (Vi)* • ***C**ryptococcus neoformans* (Mnemonic: **S**ome **K**illers **H**ave **P**retty **N**ice **S**limy **C**apsules) Others: • *Bacillus anthracis:* poly D-glutamate • *Bordetella pertussis* • *E. coli* meningeal strains: K1 capsule • *Streptococcus pyogenes:* hyaluronic acid • And many others
	M protein	Group A streptococci
	Protein A (binds Fc of IgG)	*Staphylococcus aureus*
	Pili	*Neisseria gonorrhoeae*

▼**Table A-2.1B** Microbial Invasion Mechanisms

Function	Enzyme	Microbe
Produces fibrin clot	Coagulase	• *Staphylococcus aureus* • *Yersinia pestis*
Hydrolysis of collagen	Collagenase	• *Clostridium perfringens* • *Prevotella melaninogenica*
Promotes clotting	Heparinase	• *Bacteroides* • *Prevotella melaninogenica*
Hydrolysis of ground substance	Hyaluronidase	Group A streptococci
Destroys IgA, promotes colonization of mucosal surfaces	IgA proteases	• *Haemophilus* • *Neisseria* • *Streptococcus pneumoniae*
Hydrolysis of fibrin	Kinases	• *Staphylococcus* • *Streptococcus*
Dissolves cell membranes	Lecithinase	*Clostridium perfringens*

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▼Table A-2.1C Miscellaneous Enzymes Used for Diagnosis

Function	Enzyme	Microbe
Destroys hydrogen peroxide, substrate for myeloperoxidase *(problem for CGD patients)*	***Catalase*** $H_2O_2 \rightarrow H_2O + ½ O_2$	Most important: • ***S**taphylococcus* • **N**ocardia • **E**nterobacteriaceae • ***A**spergillus* • ***L**isteria* • ***C**andida* • ***P**seudomonas* (Mnemonic: Staph '**N** **E**nterobacteriaceae **A**re **L**isted **C**atalase **P**ositive) Most anaerobes are catalase negative
Cytochrome c oxidase is the terminal electron acceptor	**Oxidase**	• *Neisseria* • Most gram negatives, except the Enterobacteriaceae
Increases local pH, contributes to kidney stones	***Urease***	• ***P**roteus* • ***U**reaplasma* • ***N**ocardia* • ***C**ryptococcus* • ***H**elicobacter* (Mnemonic: **PUNCH**)

▼Table A-2.1D Motility

Mechanism	Microbe
Flagella	• All urotropic microorganisms • *Listeria* (tumbling) • All clostridia except C. *perfringens* • Most *Bacillus* spp. except *B. anthracis* • *Giardia lamblia* (falling leaf) • *Trichomonas vaginalis* (corkscrew)
Axial filaments	Spirochetes
Pseudopodia	*Entamoeba histolytica*

▼Table A-2.1E Spore Formation

Type	Factor	Microbe
Bacteria (protection from environment)	Calcium dipicolinate, dipicolinic acid synthetase	• *Bacillus* • *Clostridium*
Fungi (protection and reproduction)		All fungi

▼Table A-2.1F Pigment Production

Pigment	Microbe
Gray, black	*Corynebacterium diphtheriae*
Yellow-orange	Photo- and scoto-chromogenic *Mycobacteria*
Blue-green, fluorescent	*Pseudomonas aeruginosa* (fluorescein and pyocyanin)
Red	*Serratia*
Yellow	*Staphylococcus aureus*

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▼**Table A-2.1G** Metabolism

O_2 Classification	Microbe
Obligate aerobes	• *Bacillus* • *Corynebacterium* • *Mycobacterium* • *Nocardia* • *Pseudomonas*
Microaerophiles	• *Borrelia* • *Campylobacter* • *Helicobacter*
Obligate anaerobes	• *Actinomyces* • *Bacteroides* • *Clostridium* • *Fusobacterium* • *Prevotella*

2 Transmission

▼**Table A-2.2A** Transmission Types and Associated Microbes

Type	Microbes
Human to Human Only	• *Chlamydia trachomatis* • *Corynebacterium diphtheriae* • *Mycobacterium tuberculosis* and *M. leprae* • *Neisseria meningitidis* and *N. gonorrhoeae* • *Rickettsia prowazekii* • *Salmonella enterica* subspecies *typhi* • *Shigella* species • *Streptococcus pneumoniae* • *Streptococcus pyogenes*
Not Transmissible Human to Human	• All anaerobes (unless they are spore-formers) • All fungi (except dermatophytes) • *Legionella pneumophila* • Mycobacteria other than tuberculosis (MOTTs)
Infections Spread by Respiratory Droplet	• *Bordetella pertussis* • Chickenpox • *Corynebacterium diphtheriae* • *Haemophilus influenzae* • Influenza and all respiratory viruses • Measles, mumps, rubella • *Mycoplasma pneumoniae* • *Neisseria meningitidis* • *Pneumocystis jirovecii* • Pneumonic plague
Infections Spread by Inhalation	• *Blastomyces* • *Chlamydophila psittaci* • *Coccidioides* • *Histoplasma* • *Legionella* • Nontuberculous mycobacteria, e.g., *M. avium-intracellulare (MAC)* • *Pseudomonas*

continued on next page

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▼**Table A-2.2A** Transmission Types and Associated Microbes *(continued)*

Type	Microbes
Infections Spread Fecal/Orally	• All cestodes • All nematodes except filaria and *Trichinella* • *Bacillus cereus* • *Campylobacter* • *Clostridium* • Enteroviruses, including poliovirus • *Giardia* • Hepatitis A and E viruses (the vowels are transmitted by the bowels) • Norwalk and Noro-like viruses • Rotavirus • *Salmonella* • *Shigella* • *Staphylococcus* • *Toxoplasma*—cat feces • *Vibrio* • *Yersinia enterocolitica* • *Yersinia pseudotuberculosis*
Parasitic Infections Transmitted by Ova*	• *Ascaris lumbricoides* • *Echinococcus granulosus/multilocularis* • *Enterobius vermicularis* • *Taenia solium* • *Toxocara canis* • *Trichuris trichiura*
Infections Spread Person-Person, Nonsexual Contact	• Dermatophytes (*Epidermophyton, Microsporum, Trichophyton*) • Epstein-Barr virus (saliva) • Hepatitis B (all body fluids) • Herpes simplex 1 • Impetigo (*Staphylococcus* and *Streptococcus*) • Molluscum contagiosum (wrestling teams) • *Staphylococcus*
Infections Spread by Sexual Contact	• *Chlamydia trachomatis* (serovars D-K, L1, 2, 3) • Cytomegalovirus • Hepatitis B virus • Hepatitis C virus • Human immunodeficiency virus • Human papilloma virus (serotypes 6 and above) • Herpes simplex 2 • *Neisseria gonorrhoeae* • *Trichomonas vaginalis* • *Treponema pallidum*
Infections That Cross the Placenta	• ***To**xoplasma gondii* • **R**ubella • **C**ytomegalovirus • **H**erpes simplex 2 • **H**uman immunodeficiency virus • **S**yphilis (Mnemonic: **ToRCHHeS**) Others that may also cross the placenta: • B19 virus • Coxsackie B • *Listeria monocytogenes* • Polio

*All other parasitic infections are transmitted in larval stage.

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▼ **Table A-2.2B** Zoonotic Organisms

Microbe	Source
Bacillus anthracis	Animal hides
Bartonella henselae	Cat scratches
Borrelia burgdorferi	Deer, mice
Brucella species	Livestock
Campylobacter fetus, C. jejuni	Poultry, livestock
Capnocytophaga canimorsus	Dog bites
Chlamydophila psittaci	Parrots, birds
Ehrlichia* and *Anaplasma spp.	Deer, mice
Francisella tularensis	Rabbits, deer
Leptospira interrogans	Animal urine: dog, rat, livestock
Listeria monocytogenes	Dairy products (goat)
Mycobacterium marinum	Fish tanks
Pasteurella multocida	Cat bites
Rabies virus	Bats, raccoons, skunks
Rickettsia rickettsiae* and most *rickettsiales	Domestic animals, deer
Salmonella enterica* all subspecies except *typhi	Poultry, reptile pets
Streptobacillus moniliformis	Rat bites
Vibrio parahaemolyticus	Fish
Vibrio vulnificus	Oysters
Y. enterocolitica	Swine
Yersinia pestis	Small rodents
Y. pseudotuberculosis	Domestic animals

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▼Table A-2.2C Arthropod Borne Organisms

Vector	Disease
Mosquito	• Dengue *(Aedes)* • Filariasis • Malaria *(Anopheles)* • Viral encephalitides (EEE, SLE, VEE, WEE, WNV) • Yellow Fever
Sandfly	• Leishmaniasis
Blackfly	• Onchocercosis
Deerfly	• Loaloasis • Tularemia
Tsetse	• African trypanosomiasis
Fleas	• Endemic typhus • Plague
True bugs (Reduviidae)	• Chagas Disease
Lice	• Endemic typhus • Relapsing fever • Trench fever
Tick (*Dermacentor*)	• Colorado tick fever • Rocky Mountain spotted fever • Tularemia
Tick (*Ixodes*)	• Babesiosis • Ehrlichiosis • Lyme Disease
Tick (*Ornithodoros*)	• Tick-borne relapsing fever
Mite (*Leptotrombium*)	• Rickettsialpox • Scrub typhus

3 Mechanisms of Pathogenesis

▼Table A-2.3A Genetic Coding

Source	Agent
Chromosome	Endotoxin
Plasmid	Most toxins and multiple drug resistances
Bacteriophage (lysogeny)	• **L**T of ETEC • **O**-antigen of Salmonella • **V**erotoxin of EHEC • **E**rythrogenic toxin of Group A Streptococcus • **D**iphtheria toxin • **C**holera toxin • **B**otulinum toxin • **S**higa toxin (Mnemonic: **LOVED CBS**)

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▼Table A-2.3B Antigenic Properties

Type	Microbe
Antigenic variation	• *Borrelia recurrentis* • Enterobacteriaceae • *Neisseria gonorrhoeae* • *Trypanosoma brucei*
Antigenic drift	HIV and any other agent that uses nucleic acids to replicate
Antigenic shift	• Viruses with segmented genomes: • Reoviridae • Orthomyxoviridae • Bunyaviridae • Arenaviridae

▼Table A-2.3C Exotoxins

Toxin	Disease	ADP ribosylating Activity?	Function
***Pseudomonas* exotoxin A**	Pseudomonal septicemia	Yes, eEF-2	Inhibits translocation
Diphtheria toxin	Diphtheria	Yes, eEF-2	Inhibits translocation
Verotoxin	EHEC	No	Inactivates 60S ribosomal subunit
Shiga toxin	Shigellosis	No	Inactivates 60S ribosomal subunit
LT of *E. coli*	Traveler's diarrhea	Yes, Gs	Increases cAMP, fluid loss
Cholera toxin	Cholera	Yes, Gs	Increases cAMP, fluid loss
Pertussis toxin	Whooping cough	Yes, Gi	Increases cAMP, causes edema, lymphocytosis and hypoglycemia
Botulinum toxin	Botulism	No	Stops release of acetylcholine, causes flaccid paralysis
Tetanus toxin	Tetanus	No	Blocks release of glycine and GABA, causes rigid paralysis
Toxic shock toxin-1	Toxic shock	No	Superantigen
Erythrogenic toxins of *Streptococcus pyogenes*	Streptococcal toxic shock	No	Superantigen

▼Table A-2.3D Heat Stable Toxins

Toxin	Stable Up To
***E. coli* ST** ***Staphylococcus aureus* enterotoxin** ***Yersinia enterocolitica* toxin**	60°C
Endotoxin	100°C

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▼Table A-2.3E Intracellular Microbes

Immunological Response	Type	Microbe
Obligate		
Require Th1 (CMI) immune response	Bacteria	• Chlamydiaceae • *Mycobacterium leprae* • Rickettsiae
	Viruses	All
	Protozoa	• *Babesia* • *Leishmania* • *Plasmodium* • *Toxoplasma* • *Trypanosoma* (in amastigote form)
Facultative		
Produce granulomas	Bacteria	• ***Y**ersinia pestis* • ***F**rancisella* • ***M**ycobacterium tuberculosis* and atypical mycobacteria • ***B**rucella* • ***B**artonella henselae* • ***S**almonella enterica* subsp. *Typhi* • ***L**isteria* • ***N**ocardia* • ***L**egionella* (Mnemonic: **Y**es **F**rank **M**ay **B**rush **B**y **S**ally **L**ist's **N**ice **L**egs)
	Fungi	*Histoplasma capsulatum*

▼Table A-2.3F Extracellular Microbes That Form Granulomas

Type	Microbe
Bacteria	*Treponema pallidum*
Parasites	*Schistosoma* spp.

▼Table A-2.3G Microbes That Cause Dystrophic Calcification

Location	Type	Microbe
Lung	Bacteria	*Mycobacterium tuberculosis*
	Fungi	• *Blastomyces* • *Coccidioides* • *Histoplasma*
Cerebral	Bacteria	• *Mycobacterium tuberculosis* • *Treponema pallidum*
	Viruses	Cytomegalovirus
	Fungi	*Cryptococcus*

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4 Diagnostic Attributes

▼**Table A-2.4A** Staining Characteristics

Stain	Microbe
Acid Fast (Kinyoun or Ziehl-Neelsen)	• *Cyclospora, Cryptosporidium, Isospora,* and *Microsporidia* forms in stool • *Mycobacterium* • *Nocardia* (partially acid fast)
Bipolar staining	• *Haemophilus influenzae* • *Francisella tularensis* • *Pasteurella multocida* • *Yersinia pestis*
Calcofluor white	Fungi
Darkfield microscopy	Spirochetes *(Treponema)*
Giemsa stain	• *Babesia* • *Leishmania* • *Plasmodium* • *Trypanosoma* • *Histoplasma capsulatum* (inside macrophages)
"Gull's" wings	*Campylobacter*
India ink	*Cryptococcus neoformans*
Kidney bean-shaped diplococci	*Neisseria*
Lancet-shaped diplococci	*Streptococcus pneumoniae*
Metachromatic staining (aniline dyes)	*Corynebacterium*
Silver stain (Dieterle)	*Legionella*
Silver stain (Gomori Methenamine)	*Pneumocystis,* fungi

▼**Table A-2.4B** Changes to Cellular Morphology

Cellular Change	Microbe
Intracytoplasmic inclusions	Most RNA viruses
Guarnieri intracytoplasmic inclusions	Poxviruses (only DNA virus that makes intracytoplasmic inclusions)
Negri intracytoplasmic inclusions	Rabies
Intranuclear inclusions	Most DNA viruses (except pox)
Cowdry intranuclear inclusions	Herpes simplex virus
Owl's eye intranuclear inclusions	Cytomegalovirus
Koilocytotic cellular change	Human papilloma virus
Syncytia formation	Herpes viruses, paramyxoviruses, HIV

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▼**Table A-2.4C** Unusual Culture Requirements

Requirement	Microbe
Cell or tissue culture	Obligate intracellular microbes
Cholesterol	*Mycoplasma*
Cysteine	• ***F**rancisella* • ***B**rucella* • ***P**asteurella* • ***L**egionella* (Mnemonic: St. **F**rancis was a **B**rother and a **P**astor in the **L**egendary **Cysteine** Chapel)
Factors X and V	*Haemophilus* (satellite phenomenon with *Staphylococcus aureus*)
Low oxygen (CO_2 incubator)	• *Campylobacter* • *Helicobacter* (microaerophiles)
Low temperature (25°C)	• *Listeria* • *Yersinia enterocolitica* (*Mycobacterium leprae* prefers cooler body temperatures but cannot be cultured)
High salt (halophilic organisms)	• Enterococci • *Staphylococcus aureus* • *Vibrio*
High temperature (42°C)	*Campylobacter*
Slow growth	• *Blastomyces* • *Coccidioides* • *Histoplasma* • *Mycobacterium* • *Mycoplasma*
Thioglycollate broth	Obligate anaerobes

▼**Table A-2.4D** Named Diagnostic Tests

Test	Microbe
CAMP test	*Streptococcus agalactiae*
Elek test	*Corynebacterium diphtheriae*
Lepromin test	*Mycobacterium leprae* (tuberculoid form)
Monospot (heterophile antibody test)	Epstein-Barr virus
Tzank smear	Herpes simplex virus
Tuberculin test (Mantoux or PPD)	*Mycobacterium tuberculosis*
VDRL (Venereal Disease Research Lab)	*Treponema pallidum*
Weil-Felix test	Rickettsiae
Widal test	Salmonellae

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5 Treatment and Prevention

▼**Table A-2.5A** Diseases Treated Prophylactically

Setting	Microbe
AIDS patients	CD4 < 200 • *Pneumocystis jirovecii* CD4 < 100 • *Histoplasma capsulatum* • *Toxoplasma gondii* CD4 < 50 • *Mycobacterium avium* complex • *Cryptococcus neoformans* • Cytomegalovirus
Household and daycare contacts	*Neisseria meningitidis*
Known exposures	• *Yersinia pestis* • Hepatitis A and B
Neonatal eyes	• *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • *Treponema pallidum*
Recent PPD conversion	*Mycobacterium tuberculosis*
Sexual contacts	• *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • *Treponema pallidum* • *Trichomonas vaginalis*
Unvaccinated contacts less than 6 years old	*Haemophilus influenzae*

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▼ **Table A-2.5B** Diseases Controlled by Vaccination

Target	Type	Vaccine
Bacterial	Toxoid	DTaP (diphtheria, tetanus, acellular pertussis)
	Subunit	• HiB: *Haemophilus influenzae* type b, polyribitol phosphate capsule conjugated to diphtheria toxoid • MCV-4: *Neisseria meningitidis*, capsular polysaccharides from types Y, W-135, C, A conjugated to diphtheria toxoid • PCV: Pediatric, capsular polysaccharides from 13 serotypes of *Streptococcus pneumoniae* conjugated to diphtheria toxoid • PPV: Adult, 23 serotypes of capsular polysaccharide from *Streptococcus pneumoniae*
Viral	Live, attenuated	• Measles • Mumps • Rotavirus • Rubella • Sabin polio • Smallpox • Varicella zoster • Yellow fever
	Live, not attenuated	Adenovirus (enteric coated serotypes 4, 7)
	Inactivated	• Hepatitis A • Influenza • Rabies • Salk polio
	Recombinant DNA	• Hepatitis B (HBsAg) • Human papilloma virus (capsid proteins from serotypes 6, 11, 16 and 18)

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Dermatology

Infections: Cutaneous/Mucocutaneous

Lesion	Keratinized layers (ringworm)	Vesicles		
			Impetigo	
Agent	• *Trichophyton* spp. (skin, hair, nails) • *Epidermophyton* spp. (skin, nails) • *Microsporum* spp. (skin, hair)	Herpes simplex	*Staphylococcus aureus*	*Streptococcus pyogenes*
Location	Skin, hair, nails	Lips (HSV 1) or genitalia (HSV 2)	Various	Various
Other clues	Reddened skin lesion in growing ring shape, raised margin; infection in nail bed or hair shaft	Often preceded by neurologic pain	Scratching skin lesion → bullous	Weeping, oozing (honey-crusted)
Pathogenesis	Fungi germinate in moist areas, invade	• Virus-rich vesicles ulcerate • dsDNA, enveloped (nuclear membrane)	Exfolatins produce bullae	Streptokinase A and B, DNAse, hyaluronidase
Dx	Wood's lamp, fluorescence; skin scraping + KOH; arthroconidia + hyphae	Cell culture, PCR, intranuclear inclusion, multinucleated cells	Catalase (+), coagulase (+), gram (+) cocci in clusters	Catalase (–), gram (+) cocci, bacitracin sensitive
Rx	Topical miconazole or oral imidazoles if hair shaft or nails infected	Acyclovir, valacyclovir, famciclovir	Nafcillin for MSSA; vancomycin for MRSA	Penicillin, macrolide

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Dermatology

Infections: Cutaneous/Mucocutaneous

Lesion	Warts			Eosinophilic dermatitis
Agent	Human Papilloma-virus (dsDNA, naked icosahedral)	*Molluscum contagiosum* (pox family, dsDNA, enveloped complex)	2° stage syphilis *Treponema pallidum* (condylomata lata)	• Dog and cat hookworms (*Ancylostoma* spp.) • Plumber's itch
Location	Plantar surfaces: HPV 1 Common warts: HPV serotypes 2, 4		Anogenital, axillary	
Other clues	Anogenital warts: • HPV 6 and 11 (most common) • HPV 16 and 18 (premalignant)	Umbilicated warts; wrestling teams; may be anogenital	Pale, moist wart-like papules	Snake-like tracks on bare skin exposed to dog/cat feces (plumber's itch, cutaneous larva migrans)
Pathogenesis	• Virus infects basal layers of skin, stimulates cells to divide • Cervical intraepithelial neoplasia • Tumor suppressor gene inactivation	Infects epidermal cells to form fleshy lesion	Lymphocytic + plasma cell infiltration	Skin penetration by larvae → death in skin → hypersensitivity (type 1)
Dx	Intranuclear inclusion bodies	Intracytoplasmic inclusions	VDRL + FTA-Abs	Clinical signs and history
Rx	Cryotherapy for common warts; imiquimod, interferon-α, cidofovir for anogenital warts	Cryotherapy	Penicillin, doxycycline, erythromycin	Topical anti-inflammatory, thiabendazole

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Dermatology

Infections: Cutaneous/Mucocutaneous

Lesion	Eosinophilic dermatitis	Suppurative dermatitis/cellulitis		
Agent	Bird schistosomes (Swimmer's itch)	*Staphylococcus aureus*	*Propionibacterium acnes*	*Pseudomonas aeruginosa*
Location	Outside of bathing suit coverage	Neck, face, axillae, buttocks	Face, neck, back, chest	• Hot tub folliculitis • Inflamed follicles from neck down • Burns
Other clues	Itching skin rash after swimming in fresh water lakes	Boils, carbuncles, furuncles	• Acne vulgaris • Adolescent	At burn site, blue-green pus; grape-like odor
Pathogenesis	Skin penetration by cercariae → death in skin → hypersensitivity (type 1)	• Coagulase makes fibrin clot • Neutrophils + bacteria → pus	Inflammation of follicles and sebaceous glands; fatty acids and peptides produced from sebum cause inflammation	Capsule inhibits phagocytosis
Dx	Clinical signs and history	Catalase (+), coagulase (+), gram (+) cocci in grape-like clusters	Clinical clues: gram (+) rod	Oxidase (+), gram (−) rod, blue-green pigment, grape odor
Rx	Topical anti-inflammatory	Nafcillin for methicillin-sensitive *S. aureus* (MSSA); vancomycin for methicillin-resistant *S. aureus* (MRSA)	Tetracycline, macrolide	Antipseudomonal beta-lactam + aminoglycoside

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Dermatology

	Infections: Cutaneous/Mucocutaneous		Infections: Subcutaneous	
Lesion	**Leishmaniasis (erosive granulomatous)**		**Suppurative surgical wounds**	
	Cutaneous	**Mucocutaneous**	**Clean**	**Dirty**
Agent	*L. tropica*	*L. braziliensis*	*Staphylococcus aureus*	Enterobacteriaceae, anaerobes
Location	Neck, hands, face	Face	Wound site	Wound site
Other clues	Military stationed in the Middle East	Immigrant from South America	Suppurating lesion, no odor to pus	Foul-smelling if anaerobes involved
Pathogenesis	Amastigotes intracellular in macrophages, proliferate and spread, granulomatous		Coagulase produces fibrin clot	Contamination from fecal flora
Dx	Finding amastigotes with flagellar pocket inside phagocytic cells in biopsy		Gram (+) cocci, catalase (+), coagulase (+)	Culture pus, treat empirically Gram (–) facultative anaerobes
Rx	Antimonials, pentamidine		Nafcillin for MSSA, vancomycin for MRSA	3rd-generation cephalosporin

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Dermatology

Infections: Subcutaneous

Lesion	Suppurative		
	Trauma with damage to blood supply	**Shallow puncture wound through tennis shoe sole**	**Ulcerating abscess**
Agent	*Clostridium perfringens* and others	*Pseudomonas aeruginosa*	*Vibrio vulnificus*
Location	Wound site	Feet	Hands
Other clues	Dirty wound, crushing injury	Blue-green pus, fruity odor	Cellulitis following contact with saltwater or oysters
Pathogenesis	Alpha toxin (lecithinase) gas production, edema, cytotoxicity	Capsule inhibits phagocytosis	Cytolytic compounds, antiphagocytic polysaccharides
Dx	Nagler reaction, anaerobic, gram (+) rod, spore forming	Oxidase (+), gram (–) rod, blue-green pigments	Green colonies on TCBS agar (alkaline), gram (–) rod, oxidase (+)
Rx	Debridement, clindamycin, chloramphenicol, tetracycline	Antipseudomonal β-lactam + aminoglycoside	Tetracycline, aminoglycosides

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Dermatology

Infections: Subcutaneous

Lesion	Suppurative (mycetoma) Swollen abscess with pain, sinus tract formation, yellow granules in exudate		
Agent	Non-myotic, *Actinomyces israelii*; "lumpy jaw"; actinomycosis	• Non-mycotic, *Nocardia asteroides* (lung) • *N. braziliensis*	Eumycotic, *Sporothrix schenckii* (rose gardener's disease)
Location	Carious teeth, dental extraction, or trauma to jaw	Hands, limbs	Hands, arms
Other clues	Dental trauma, jaw line	Subcutaneous swelling, sinus tract formation, granules (mycetoma)	Solitary or lymphocutaneous lesions; rose gardeners or florists; sphagnum moss
Pathogenesis	Unknown, invasive	Unknown	Unknown
Dx	Culture pus, gram (+), anaerobic, filamentous branching rods, non-acid fast	Partially acid-fast, branching filaments, aerobic	Cigar-shaped yeast in pus
Rx	Penicillin, debridement, doxycycline, clindamycin	Sulfonamide, sulfa antibiotics; carbapenem for resistant cases	Potassium iodide, ketoconazole

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Dermatology

Infections: Subcutaneous

Lesion	Suppurative animal bite wounds			
Agent	*Pasteurella multocida*	*Eikenella corrodens*	*Capnocytophaga canimorsus*	*Streptobacillus moniliformis* and *Spirillum minus*
Location	Bite wound			
Other clues	Bite of various animals	Human bite, fist fight, barroom brawl	Dog bite	Rat bite
Pathogenesis	Capsule	Pili, phase variation	Sialidase allows adherence to host cells	Endotoxin
Dx	Gram (–) rods (bite wounds are not generally cultured)	Gram (–) oral floral	Gram (–) fusiform	Gram (–) pleomorphic rod
Rx	Amoxicillin/ clavulanate	3rd-generation cephalosporins, fluoroquinolones	Amoxicillin/ clavulanate	Penicillin G or V

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Dermatology

Infections: Subcutaneous

Lesion	Suppurative			Granulomatous
	Acute mastitis	Malignant pustule (anthrax eschar)	Malignant pustule (ecthyma gangrenosum)	(fishtank granuloma)
Agent	*Staphylococcus aureus, Streptococcus*	*Bacillus anthracis*	*Pseudomonas aeruginosa*	*Mycobacterium marinum*
Location	Breast, unilateral	Various	Various	Hands
Other clues	Early nursing mother	Pustule → dark-red, fluid-filled, tumor-like lesion → necrosis → black eschar surrounded by red margin; postal worker or wool importer	Pseudomonal septicemia	Tropical fish enthusiasts; granulomatous lesion
Pathogenesis	Fissures in nipples predispose to invasion of normal flora	• Poly-D-glutamate capsule, exotoxin causes edema, cell death • Three-component toxin	Endotoxin	Trauma + water exposure → intracellular organism, granulomas form
Dx	Culture pus, gram (+) cocci	Gram (+), spore-forming, encapsulated rods	Blood culture, gram (–), oxidase (+), produces blue-green pigments, fruity odor	Biopsy, slow growing, acid-fast bacilli
Rx	Penicillin, surgical drainage	Ciprofloxacin, penicillin	Susceptibility testing necessary	Clarithromycin initially, then antimycobacterial therapy

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Dermatology

Infections: Subcutaneous

Lesion	**Granulomatous**	**Nodular**	**Granulomatous**
	Leprosy		**Cat scratch disease**
Agent	*Mycobacterium leprae* (tuberculoid form)	*Mycobacterium leprae* (lepromatous form)	*Bartonella henselae*
Location	Cooler areas of skin		Various
Other clues	• Immigrant from Asia • Blotchy, red lesions with anesthesia; facial and cooler areas of skin	• Immigrant from Asia • Numerous nodular lesions; leonine facies	Exposure to cats
Pathogenesis	Cell-mediated immunity kills intracellular organisms, damages nerves	Humoral immunity elicited does not stop growth of organisms	• Facultative intracellular • Gram (–) envelope
Dx	Acid-fast, intracellular bacilli in punch biopsy, (+) lepromin test	Acid-fast, intracellular bacilli in punch biopsy, (–) lepromin test	Clinical; biopsy of lymph node with stellate granulomas
Rx	Dapsone and rifampin	Dapsone, clofazimine, rifampin	Rifampin, ciprofloxacin, gentamicin, TMP-sulfamethoxazole

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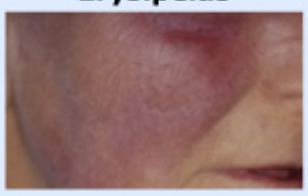
Dermatology

Rashes

Type	Erythematous		Erythematous + Macular	
Disease	Lyme disease	Erysipelas 	Toxic shock syndrome	Scarlet fever
Agent	*Borrelia burgdorferi* (No. 1 vector-borne disease in U.S.)	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Streptococcus pyogenes*
Location	• Originates at site of tick bite • Concentric rings (bull's-eye, target)	Raised facial butterfly wing	• Diffuse, sunburn-like • Trunk and neck → extremities with desquamation on palms and soles	Trunk and neck → extremities (spares palms and soles); sandpaper-like
Other clues	Fever, headache, myalgia, Bells palsy	Dermal pain, edema, rapid spread	Acute onset, fever, myalgia, pharyngitis, vomiting, diarrhea; hypotension, multiorgan failure	Sore throat, fever, nausea
Pathogenesis	Invades skin and spreads to involve heart, joints, and CNS; arthritis is type III hypersensitivity	M protein inhibits phagocytosis, erythrogenic exotoxins, hyaluronidase	TSST-1 (superantigen)	Exotoxins A-C (superantigens)
Dx	Serology; EIA + Western blot	Catalase (–), gram (+) cocci, bacitracin-sensitive	Gram (+), catalase (+), coagulase (+) cocci	Gram (+), catalase (–) cocci
Rx	Doxycycline, ceftriaxone	Penicillin, macrolide	Nafcillin, oxacillin; vancomycin in penicillin allergy	Penicillin, clindamycin

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Dermatology

Rashes

Type	Maculopapular		Papular
Disease	**Secondary syphilis**	**Measles**	**2° syphilis (condylomata lata)**
Agent	*Treponema pallidum*	Rubeola virus; negative sense RNA virus, nonsegmented = Paramyxovirus	*Treponema pallidum*
Location	Generalized bronzing rash involving the palms and soles	Head → entire body	Anogenital, axillary
Other clues	Fever, lymphadenopathy, malaise, sore throat, splenomegaly, headache, arthralgias, IV drug abusing females	Cough, coryza, conjunctivitis, fever, Koplik spots, bronchopneumonia, ear infections, unvaccinated child	Bronzing rash, IV drug abusing females
Pathogenesis	Endotoxin	T cell destruction of virus-infected cells in capillaries causes rash	Endotoxin
Dx	Serology: VDRL (nonspecific), FTA-ABS (specific)	Virus cultures, serology	VDRL + FTA-ABS
Rx	Penicillin, doxycycline, erythromycin	Supportive	Penicillin, doxycycline, erythromycin

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Dermatology

Rashes

Type	Vesicular	Vesicular + Pruritic	Vesicular + Painful
Disease	Scalded skin syndrome	Chickenpox	Shingles
Agent	*Staphylococcus aureus*	Varicella-Zoster virus (Herpesviridae, dsDNA)	Varicella-Zoster virus (Herpesviridae, dsDNA)
Location	Trunk and neck → extremities, except tongue and palate; large bullae and vesicles precede exfoliation	• Generalized with involvement of mucous membranes • Asynchronous rash, unvaccinated child	Unilateral vesicular rash following a dermatome
Other clues	Abscess or another site of infection	Fever, pharyngitis, malaise, rhinitis, exanthem	Fever, severe nerve pain, pruritus, 50– to 60–year–old patient
Pathogenesis	• Exfoliatins • Exotoxins	Virus replicates in mucosa and is latent in dorsal root ganglia	Reactivation of latent infection
Dx	Gram (+), catalase (+), coagulase (+) cocci	Tzanck smear (find syncytia), Cowdry type A intranuclear inclusions, PCR	Tzanck smear (find syncytia), Cowdry type A intranuclear inclusions, PCR
Rx	Nafcillin, oxacillin; vancomycin in penicillin allergic patients	Supportive, avoid aspirin due to Reye syndrome	Acyclovir, famciclovir, valacyclovir

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Dermatology

Rashes

Type	Petechial/Purpuric		
Disease	Meningococcemia	Rocky Mountain spotted fever	Epidemic typhus
Agent	*Neisseria meningitidis*	*Rickettsia rickettsii*	*Rickettsia prowazekii*
Location	Generalized	Ankles and wrists → generalized with palms and soles	Trunk → extremities; spares palms, soles, and face
Other clues	Abrupt onset, fever, chills, malaise, prostration, exanthem → shock	Fever, rash, headache, myalgias, and respiratory symptoms	Fever, rash, headache, myalgias, and respiratory symptoms
Pathogenesis	Endotoxin (overproduces outer membrane fragments)	Infects endothelial cells; endotoxin	Endotoxin
Dx	Gram (–) diplococcus on chocolate agar; LPA for capsular antigens	Serology, Weil-Felix	Serology, Weil-Felix
Rx	Ceftriaxone	Doxycycline, chloramphenicol	Doxycycline, chloramphenicol

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Hematology

Hematologic Changes Associated With Infectious Disease

Blood Cell Counts—Increased

Condition	Neutrophilia (↑ PMNs)	Eosinophilia (↑ eosinophils)		Mononucleosis (↑ lymphocytes + monocytes)
Associated agent	Many extracellular bacterial infections	Allergy	Helminths during migrations	Intracellular organisms: viruses, *Listeria, Legionella, Leishmania, Toxoplasma*
Other clues	↑ Bands, "left shift"	Immediate onset of symptoms after exposure	Exposure to source of helminth parasite	Depends on agent
Pathogenesis	*N*-formyl methionyl peptides are chemotactic for PMNs	ECF-A released by mast cells attracts eosinophils	Parasites release allergens	Intracellular organisms elicit Th1 cells and CMI
Dx	Culture, Gram stain	Skin testing: wheal and flare	Depends on agent	
Rx	Depends on agent	Antihistamines	Depends on agent	

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Hematology

Blood Cell Counts—Increased

Condition	Mononucleosis (↑ lymphocytes + monocytes)		Lymphocytosis
Associated agent	Infectious mononucleosis: Epstein-Barr virus	Infectious mononucleosis: CMV	*Bordetella pertussis*
Other clues	Fever, fatigue, sore throat, lymphadenopathy, myalgia, headache, heterophile (+), Downey type II cells (reactive T cells), young adult, possible splenic rupture	Fever, fatigue, sore throat, lymphadenopathy, myalgia, headache, heterophile (–)	• Lymphocytosis with hacking cough • Unvaccinated child, hypoglycemic
Pathogenesis	Virus infects B lymphocytes via CD21; CTLs respond to kill virus-infected cells	Virus infects fibroblasts; CTLs respond to kill virus-infected cells	Tracheal cytotoxin, fimbrial antigen, endotoxin, ↓ chemokine receptors
Dx	• Monospot (+) • Complete blood count	• Monospot (–) • Virus culture	Gram (–) rod, culture Bordet-Gengou agar or serology
Rx	Supportive	Ganciclovir (severe cases)	Erythromycin, antitoxin

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Hematology

Blood Cell Counts—Decreased

Condition	Anemia		
	Normocytic to Microcytic	**Microcytic and hypochromic (iron-deficiency anemia)**	**Megaloblastic**
Associated agent	Chronic infections	*Ancylostoma, Necator, Trichuris*	*Diphyllobothrium latum*
Other clues	Depends on agent	Abdominal pain, blood in stool	• Ingestion of raw fish • Great Lakes Region
Pathogenesis	Bacteria chelate iron	Hookworms suck blood; *Trichuris* damages mucosa	Parasite absorbs B12
Dx	Culture, Gram stain	Golden brown, oval eggs; eggs with bipolar plugs	Operculated eggs in stool
Rx	Depends on agent	Mebendazole	Praziquantel

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Hematology

Blood Cell Counts—Decreased

Condition	Anemia: Hemolytic	Th Lymphocytes ($CD4^+$ cells)
Associated agent	*Plasmodium* spp.	HIV
Other clues	• Travel to tropics, parasites in RBCs • Patient with cyclic or irregular fever, ↓ hemoglobin and hematocrit	• Lymphadenopathy • Opportunistic infections
Pathogenesis	• Parasite lyses RBC • Autoimmune RBC destruction	Virus infects and destroys $CD4^+$ T cells and macrophages
Dx	Rings/trophozoites in blood film	ELISA, Western blot
Rx	Chloroquine, etc. (considerable drug resistance), followed by primaquine if *P. vivax* or *P. ovale*	NRTIs, NNRTIs, protease inhibitors, fusion inhibitors, CCR5 antagonists, integrase inhibitors

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Bone and Joint

Osteomyelitis

(Fever, bone pain, erythema, swelling)

Patient setting	No. 1 overall in adults, children, and infants without major trauma or special conditions	Sickle cell anemia	Trauma	Immigrants from Indian subcontinent; spine, hip, knee, hands
Agent	*Staphylococcus aureus*	*Salmonella* spp.	*Pseudomonas aeruginosa*	*Mycobacterium tuberculosis*
Pathogenesis	Hematogenous spread → lytic bone lesions, lytic toxins	HbS patients are functionally asplenic and cannot kill bloodborne pathogens	Capsule protects against phagocytosis	Tuberculous granuloma erodes into bone
Dx	Blood culture or bone biopsy, gram (+), catalase (+), coagulase (+)	Gram (−), oxidase (−), nonlactose fermenting	Gram (−), oxidase (+), blue-green pigments, grape odor	Auramine screen for acid-fast bacilli
Rx	Nafcillin, 3rd-generation cephalosporin, IV vancomycin	3rd-generation cephalosporin, fluoroquinolones, chloramphenicol	Antipseudomonal β-lactam + aminoglycoside, or carbapenem + antipseudomonal fluoroquinilone + aminoglycoside	Multiple drug therapy

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Bone and Joint

Infectious Arthritis

(Pain, low-grade fever, reduced joint mobility, swelling)

Patient setting	High neutrophil count in joint fluid			Chronic onset, monoarticular, weightbearing joints
	No. 1 overall (except in the 15–40 age group)	15–40 years, mono- or polyarticular	Prosthetic joint	
Agent	*Staphylococcus aureus*	*Neisseria gonorrhoeae*	Coagulase-negative staphylococci	*M. tuberculosis* or fungal
Pathogenesis	Coagulase inhibits phagocytosis	Pili mediate adherence and inhibit phagocytosis	Biofilm allows adherence to Teflon	Granulomas erode into bone
Dx	Gram (+), coagulase (+) cocci, catalase (+)	Gram (–) diplococcus; ferments glucose but not maltose	Gram (+), catalase (+) cocci, coagulase (–)	Acid-fast bacillus or auramine stain, fungus stain
Rx	Nafcillin, 3rd-generation cephalosporin, IV vancomycin	Ceftriaxone	Nafcillin, 3rd-generation cephalosporin	Multiple drug therapy

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Bone and Joint

Post Infectious Arthritis

Patient setting	Immune complex (type III hypersensitivity)	Reiter syndrome (ureitis, arthritis, conjunctivitis)	
Agent	Rubella and hepatitis B, Parvovirus, Lyme disease	*Salmonella, Shigella, Campylobacter, Yersinia enterocolitica* (1–3 weeks following GI infection)	*Chlamydia trachomatis* (1–3 weeks following STI)
Pathogenesis	Immune complex mediated (type III hypersensitivity)	Molecular mimicry between microbes and joint proteins	
Dx	Detect immune complexes	Clinical	
Rx	Immunosuppressive therapy	Symptomatic	

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Eye

Eye Infections

Location	Eyelid			Conjunctiva
Type	Stye	Swelling		Conjunctivitis
Age group	All			Neonate
Agent	• *Staphylococcus aureus* • *Propionibacterium acnes*	*Trypanosoma cruzi*	*Trichinella spiralis*	*Chlamydia trachomatis*, serovars D-K
Other clues	Painful, purulent	Unilateral inflammation at bite site; travel to Central or South America	Bilateral eyelid swelling, >10% eosinophilia, fever, muscle pain; earlier GI Sx	Red, itchy eye, pus; onset 5–10 days
Pathogenesis	Abscess formation	Inflammation due to parasite invasion	Edema from larval migration into muscle	Intracellular granulomatous
Dx	Clinical	Blood film	Muscle biopsy	Intracytoplasmic inclusion bodies in scrapings
Rx	Supportive	Benznidazole, nifurtimox	Supportive	Erythromycin

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Eye

Eye Infections

Location	Conjunctiva			
Type	Conjunctivitis			
Age group	Neonate		Adult (bacterial)	
Agent	*Nisseria gonorrhoeae*	*Staphylococcus aureus*	*Chlamydia trachomatis*, serovars A-C; Trachoma	• *Staphylococcus aureus* • Group A Strep • *Streptococcus pneumoniae*, all gram (+) • *Haemophilus influenzae* • *H. aegyptius*
Other clues	Red, itchy eye, pus onset 5–10 days	"Sticky eye"	Entropion, intracytoplasmic inclusions	Red eye, pus
Pathogenesis	Neutrophilic infiltrate		Intracellular granulomatous	Neutrophilic infiltration
Dx	Gram (–) diplococci in PMNs	Gram (+), catalase (+), coagulase (+) cocci	Intracytoplasmic inclusion bodies in scrapings	Clinical
Rx	Erythromycin	Tetracycline ointment	Erythromycin	Tetracycline ointment

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Eye

Eye Infections

Location	Conjunctiva	Cornea		
Type	Conjunctivitis	Keratitis		
Age group	Adult (viral)	Neonate		Adult
Agent	Adenovirus (more common than bacterial pink eye)	*Treponema pallidum*	*Toxoplasma gondii*	*Acanthamoeba* spp.
Other clues	Red, itchy* thin exudate, photophobia	Mother is IV drug user	Mother with primary toxoplasmosis in pregnancy	Contaminated contact lens solution
Pathogenesis	Viral cytopathogenesis	Unknown	Intracellular organism proliferates in immunoprivileged sites	Free-living amebae introduced into eye erode cornea
Dx	Clinical	Clinical	Serology ↑ IgM anti-Toxoplasma	
Rx	Eye lubricant	Penicillin	Pyrimethamine, sulfadiazine	

*Distinguish from allergic: Allergic conjunctivitis subsides with elimination of allergen.

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Eye

Eye Infections

Location	Choroid and retina	
Type	Chorioretinitis	
Age group	Neonate or AIDS	
Agent	*Toxoplasma gondii*	*Cytomegalovirus*—No. 1 in utero infection in U.S.
Other clues	Mother with primary toxoplasmosis during gestation or AIDS patient; AIDS patient at CD4 count <100	Mother with flu-like syndrome during pregnancy; AIDS patient at CD4 count <50/mm
Pathogenesis	Intracellular organism proliferates in immunoprivileged sites	Viral proliferation in immunoprivileged sites
Dx	Clinical; focal necrotizing chorioretinitis	Owl's eye inclusions in biopsy, urine, PCR
Rx	Pyrimethamine, sulfadiazine	Ganciclovir; damage irreversible

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Ear, Nose, Throat, and Respiratory

ENT and Upper Respiratory Infections

Syndrome	Malignant otitis externa	Otitis externa		
Agent	*Pseudomonas aeruginosa*	*Staphylococcus aureus* (from normal flora)	*Candida albicans* (from normal flora)	*Pseudomonas aeruginosa* (from water sources)
Other clues	Severe ear pain in diabetic; life-threatening, pain on moving pinna	Purulent lesion	• Ear pain • Creamy exudate	• Swimmer—blue-green pus • Fruity odor
Pathogenesis	Capsule	Normal flora enter abrasions		Capsule protects against phagocytosis
Dx	Gram (–) rod, oxidase (+), blue-green pigments, fruity odor	Gram (+), catalase (+), coagulase (+)	Gram (+) yeast, germ tube test	Gram (–) rod, oxidase (+), blue-green pigments
Rx	Susceptibility testing	β-lactamase-resistant penicillin	Nystatin, miconazole	Susceptibility testing

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Ear, Nose, Throat, and Respiratory

ENT and Upper Respiratory Infections

Syndrome	Otitis externa	Acute otitis media		
Agent	*Proteus* (from water sources)	*Streptococcus pneumoniae* (No. 1 overall)	*H. influenzae* (nontypeable)	*Moraxella catarrhalis*
Other clues	Swimmer—urease (+), gram (–) bacillus	Red, bulging tympanic membrane, fever 102–103°F; pain goes away if drum ruptures or if ear tubes are patent		
Pathogenesis	Capsule protects against phagocytosis	Capsule, IgA protease	Capsule, IgA protease, endotoxin	β-lactamase producer
Dx	Gram (–) rod, urease (+), oxidase (–), swarming motility	• Treat empirically • Gram (+) coccus, catalase (–)	• Treat empirically • Gram (–) rod, chocolate agar	• Treat empirically • Gram (–) diplococcus
Rx	Susceptibility testing	Penicillin	Amoxicillin	Ceftriaxone

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Ear, Nose, Throat, and Respiratory

ENT and Upper Respiratory Infections

Syndrome	Sinusitis			
Agent	*Streptococcus pneumoniae* (No. 1 overall)	*Haemophilus influenzae*	*Moraxella catarrhalis*	Zygomycota *(Mucor, Rhizopus, Absidia)*
Other clues	Sinus pain, low-grade fever			Ketoacidotic diabetic, leukemic patient, black nasal discharge
Pathogenesis	Capsule, IgA protease	Capsule, IgA protease, endotoxin	β-lactamase producer	Fungi invade brain through cavernous sinus
Dx	Gram (+) coccus, catalase (–)	Gram (–) rod, chocolate agar	Gram (–) coccus, butyrate esterase producer	Clinical, culture nasal discharge
Rx	Penicillin	Amoxicillin	Ceftriaxone	Amphotericin B

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Ear, Nose, Throat, and Respiratory

ENT and Upper Respiratory Infections

Syndrome	Oral cavitary disease		Sore throat (bacterial; abscessing exudative)
Agent	*Candida albicans*	*Fusobacterium* + *Treponemes*	*Streptococcus pyogenes*
Other clues	Sore mouth with thick, white coating that can be scraped off easily to reveal painful red base*; AIDS, IC, antibiotics, vitamin C deficiency	Acute necrotizing ulcerative gingivostomatitis, painful mouth (Vincent angina)	Inflamed tonsils/pharynx, abscesses; cervical lymphadenopathy, fever, sandpaper rash
Pathogenesis	Overgrowth of normal flora, immunocompromised, overuse of antibiotics	Overgrowth of normal flora	Exotoxins A-C (superantigens)
Dx	Gram (+) yeast, germ tube test	Spirochete + fusobacterium	Rapid antigen test; gram (+), catalase (−) coccus; β-hemolytic, bacitracin sensitive
Rx	Nystatin, miconazole	Debridement	Penicillin

*Contrast to leukoplakia, which cannot be dislodged.

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Ear, Nose, Throat, and Respiratory

ENT and Upper Respiratory Infections

Syndrome	Sore throat			Common colds
	Bacterial; abscessing exudative	Viral; clear, serous exudate		
Agent	*Corynebacterium diphtheriae*	Coxsackie A	Epstein-Barr virus	• Rhinoviruses (summer-fall) • Coronaviruses (winter-spring)*
Other clues	Low-grade fever with gradual onset of obstructive laryngotracheitis; bull neck, elevated BUN; abnormal ECG; unvaccinated, dislodged membrane bleeds profusely	White papules with red base on posterior palate and pharynx; fever	Severe fatigue, lymphadenopathy, fever, +/- rash	Rhinitis, sneezing, coughing; seasonal peaks
Pathogenesis	Diphtheria toxin inactivates eEF-2 in heart, nerves, epithelium; pseudomembrane → airway obstruction when dislodged	Unknown	Infects B lymphocytes by attachment to CD21, causes ↑ Tc	Virus attaches to ICAM-1 on respiratory epithelium
Dx	Gram (+) nonmotile rod, Loeffler medium, ELEK test	Serology	Virus culture or PCR	Clinical
Rx	Penicillin, antitoxin	Supportive	Heterophile (+) (Monospot test); mononucleosis; 70% lymphocytosis (Downey type II cells=Tc)	Supportive

*Many other causes—human metapneumovirus, adenovirus, etc.

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Ear, Nose, Throat, and Respiratory

ENT and Middle Respiratory Infections

Syndrome	Epiglottitis	Laryngotracheitis, laryngotracheobronchitis	Bronchitis, bronchiolitis	
Agent	*Haemophilus influenzae*	Parainfluenza virus	Respiratory syncytial virus	*Mycoplasma pneumoniae*
Other clues	Inflamed epiglottis; patient often 2–3 years old and unvaccinated	Croup; infant with fever, sharp barking cough, inspiratory stridor, hoarse phonation	Wheezy; infant or child ≤5 years old	>5 years old
Pathogenesis	Capsule (polyribitol phosphate) inhibits phagocytosis; IgA protease	Viral cytolysis; multinucleated giant cells formed	Fusion protein creates syncytia	Release of O_2 radicals causes necrosis of epithelium
Dx	Gram (–) rod, chocolate agar (requires hemin and NAD)	Detect virus in respiratory washings	Direct immunofluorescence for viral Ags	Slow growth on Eaton medium, cold agglutinins
Rx	Ceftriaxone	Ribavirin	Ribavirin, palivizumab to high risk contacts	Symptomatic

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Ear, Nose, Throat, and Respiratory

	ENT and Middle Respiratory Infections	ENT and Lower Respiratory Infections		
Syndrome	**Bronchitis, bronchiolitis**	**Pneumonia, typical (lobar consolidation, productive cough, high fever)**		
Agent	*Bordetella pertussis*	*Streptococcus pneumoniae*	*Staphylococcus aureus*	Anaerobes, mixed infection (*Bacteroides, Fusobacterium, Peptococcus*)
Other clues	Whooping cough: Unvaccinated, inspiratory stridor, cough >2 weeks afebrile	Adults, rust-colored sputum; lobar pneumonia or, less commonly, bronchopneumonia (No. 1 overall)	Adults, aspiration or ventilator; nosocomial; salmon-colored sputum	Foul-smelling sputum, aspiration possible
Pathogenesis	Toxins cause edema, lymphocytosis, hypoglycemia	Capsule antiphagocytic, IgA protease	Abscessing, necrotizing	Aspiration of vomitus → enzyme damage → anaerobic foci
Dx	Serology	Gram (+) diplococcus, catalase (−), α-hemolytic, lysed by bile, inhibited by optochin	Gram (+), catalase (+), coagulase (+) coccus	Culture of sputum
Rx	Erythromycin + antitoxin	3rd-generation cephalosporin, azithromycin	MSSA: amoxicillin + clavulanate MRSA: vancomycin	Empiric antibiotic therapy (amoxicillin/clavulanate, gentamicin)

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Ear, Nose, Throat, and Respiratory

ENT and Lower Respiratory Infections

Syndrome	Pneumonia, typical (lobar consolidation, productive cough, high fever)		Acute or chronic pneumonia with granulomatous inflammation + calcifying lesions	
Agent	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Mycobacterium tuberculosis*	*Histoplasma capsulatum*
Other clues	Neutropenic patients, burn patients, CGD, CF	Alcoholic with aspiration, facultative anaerobic, gram (–) bacterium with large capsule, currant jelly sputum	• Over 55 years, HIV (+), or immigrant from developing country • Fever, night sweats, weight loss, hemoptysis	Dusty environment with bird or bat fecal contamination (Missouri chicken farmers, Ohio River drainage), AIDs
Pathogenesis	Opportunist, endotoxin	Capsule protects against phagocytosis	Facultative intracellular parasite → cell-mediated immunity and DTH	Facultative intracellular → granuloma formation
Dx	Gram (–) rod, oxidase (+), blue-green pigments	Gram (–) rod, lactose fermenting, oxidase (–)	Auramine-rhodamine stain of sputum, acid-fast bacilli	Intracellular yeast cells in sputum
Rx	Sensitivity testing required	Susceptibility testing necessary	Multidrug therapy	Amphotericin B

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Ear, Nose, Throat, and Respiratory

ENT and Lower Respiratory Infections

Syndrome	Acute or chronic pneumonia with granulomatous inflammation + calcifying lesions		Atypical pneumonia of bacterial origin (interstitial pneumonitis without consolidation; dry cough, low fever)	
Agent	*Blastomyces dermatitidis*	*Coccidioides immitis*	*Mycoplasma pneumoniae* (most common in school-age children)	*Legionella pneumophila*
Other clues	Rotting, contaminated wood, same endemic focus as *Histoplasma* + East Coast states (N.C. and S.C.), AIDS	Desert sand of Southwest U.S., AIDS	Pneumonia teens/ young adults; bad hacking, dry cough; "walking pneumonia"	Air-conditioning exposure; common showers; especially >50 years; heavy smoker, drinker
Pathogenesis	Acute, chronic lung infection, dissemination		Adhesin causes adhesion to mucus; oxygen radicals cause necrosis of epithelium	Intracellular in macrophages, granulomatous inflammation
Dx	Broad-based budding yeast cells in sputum or skin	Endospores in spherules in tissues	Serology, cold agglutinins	Direct fluorescent antibody
Rx	Ketoconazole	Amphotericin B	Tetracycline, erythromycin	Erythromycin

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Ear, Nose, Throat, and Respiratory

ENT and Lower Respiratory Infections

Syndrome	Atypical pneumonia (interstitial pneumonitis without consolidation; dry cough, low fever)			
	Bacterial origin	Viral origin		Fungal origin
Agent	*Chlamydophila psittaci*	Influenza virus	Measles	*Pneumocystis jirovecii (carinii)*
Other clues	Bird exposure +/- hepatitis	Primary influenza pneumonia	Poorly nourished, unvaccinated baby/ child; giant cell pneumonia with hemorrhagic rash, Koplik spots	AIDS patients or premature infants with staccato cough; "ground glass" x-ray; honeycomb exudate with silver-staining cysts
Pathogenesis	Obligate intracellular	Cytolysis in respiratory tract; cytokines contribute; secondary infections common	• Cytolysis in lymph nodes, skin, mucosa • Syncytia → giant cell pneumonia	Attaches to type I pneumocytes, causes excess replication of type II pneumocytes
Dx	Direct fluorescent antibody, intracytoplasmic inclusions	Virus culture, serology hemagglutinin titer	Serology	Silver-staining cysts in alveolar lavage
Rx	Tetracycline, erythromycin	Amantadine, rimantadine	Supportive	Trimethoprim sulfamethoxazole, pentamidine

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Ear, Nose, Throat, and Respiratory

ENT and Lower Respiratory Infections

Syndrome	Sudden acute respiratory syndromes	
Agent	SARS coronavirus	Hantavirus (Sin Nombre)
Other clues	Travel to Far East, Toronto, winter, early spring	"Four Corners" region (CO, UT, NM, AZ), spring, inhalation of rodent urine
Pathogenesis	Replication in cells of upper respiratory tree	Virus disseminates to CNS, liver, kidneys, endothelium
Dx	Serology, virus isolation	
Rx	Ribavirin, experimental	Ribavirin

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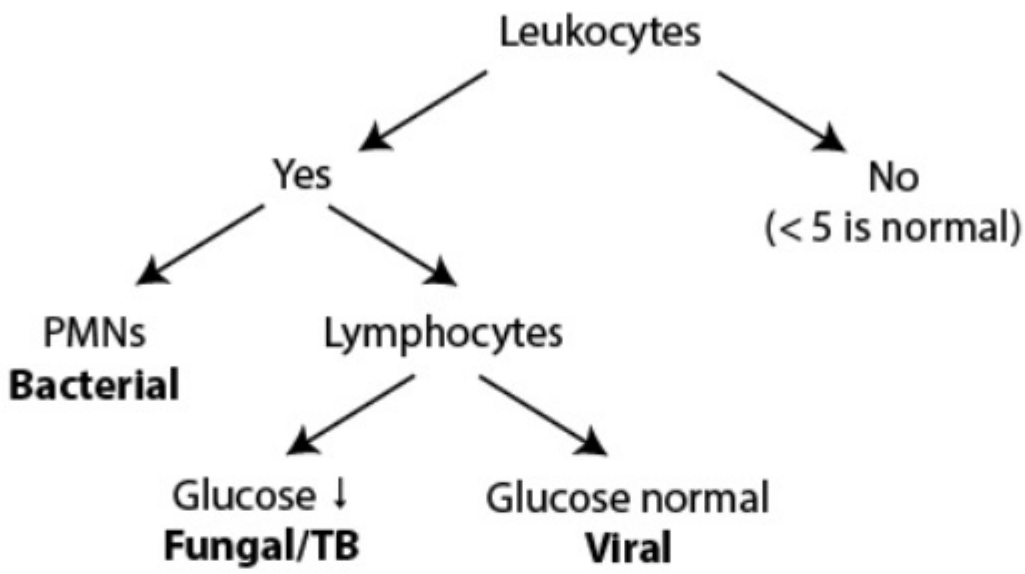
Central Nervous System

Evaluation of CSF



CSF Parameters in Meningitis

Condition	Normal values	Purulent (bacterial)	Aseptic (viral)	Granulomatous (mycobacterial/ fungal)
Pressure (mmH_2O)	70–180	Markedly elevated	Slightly elevated	Moderately elevated
Cells/µL	<5 lymphocytes	Up to 90,000 neutrophils	100–1,000 most lymphocytes	100–1,000 most lymphocytes
Glucose (mg/dL)	45–85 (50%–70% of blood glucose)	Decreased (<45)	Normal	Decreased (<45)
Proteins (mg/dL)	15–45	Increased (>50)	Increased (>50)	Increased (>50)

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Central Nervous System

Meningitis

(Headache, fever, nuchal rigidity, obtundation, coma, neutrophilic exudate. May develop hydrocephalus herniation, cranial nerve damage.)

Age	Neonate		
Type	Bacterial		
Agent	*Streptococcus agalactiae* (No. 1 cause)	*Escherichia coli* (No. 2 cause)	*Listeria monocytogenes* (No. 3 cause)
Other clues	Difficult labor, bulging fontanelles, irritability	Bulging fontanelles	Bulging fontanelles
Pathogenesis	Encapsulated; passed from maternal normal flora	Endotoxin; passed from maternal normal flora	Passed from maternal normal flora
Dx	CSF—gram (+) cocci	CSF—gram (–) rods	CSF—gram (+) rods
Rx	Ampicillin, penicillin G	Cefotaxime	Ampicillin with or without aminoglycoside

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Central Nervous System

Meningitis

(Headache, fever, nuchal rigidity, obtundation, coma, neutrophilic exudate. May develop hydrocephalus, herniation, cranial nerve damage.)

Age	3 months → 2 years		3 months → young adult	Adult
Type	Bacterial; unvaccinated	Bacterial; vaccinated		Bacterial
Agent	*Haemophilus influenzae* type b	*Streptococcus pneumoniae*	*Neisseria meningitidis*	*Streptococcus pneumoniae*
Other clues	Immigrant family, religious objections to vaccination, gram (–) bacilli, chocolate agar	Very young or very old, immunocompromised	Adolescent, dorm or barracks living, extremely acute onset, petechial rash	Very young or very old, immunocompromised
Pathogenesis	Capsule, endotoxin, IgA protease	IgA protease, capsule, PMN infiltration	Endotoxin—overproduces outer membrane fragments, IgA protease	IgA protease capsule, PMN infiltration
Dx	• Quellung or latex particle agglutination (LPA) • Chocolate agar—requires factors X + V	Quellung, LPA to serotype capsule, gram (+), catalase (–), α-hemolytic, optochin sensitive, bile soluble	LPA, culture chocolate agar, gram (–) diplococcus	Quellung, LPA to serotype capsule, gram (+), catalase (–), α-hemolytic, optochin sensitive, bile soluble
Rx	Ceftriaxone	Cefotaxime, vancomycin	Penicillin G, chloramphenicol, cefotaxime, ceftriaxone	Cefotaxime, vancomycin

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Central Nervous System

Meningitis

(Headache, fever, nuchal rigidity, obtundation, coma, neutrophilic exudate. May develop hydrocephalus, herniation, cranial nerve damage.)

Age	Adult			Any
Type	Bacterial; immunocompromised		Fungal; immuno-compromised	Viral; aseptic
Agent	*Listeria monocytogenes*	*Mycobacterium tuberculosis* or MAI	*Cryptococcus neoformans* (No. 1 cause)	Enterovirus most common
Other clues	Ingestion of unpasteurized dairy, renal transplant, leukemic patient	Basal surface of brain and dura, frequent in AIDS	Acquired from bird guano, diffuse meningoencephalitis	Leptomeningeal inflammation, lymphomonocytic infiltrates, depressed consciousness, low mortality
Pathogenesis	Facultative intracellular	Dissemination from lung	Dissemination from lung	Unknown fecal/oral spread gut → blood → brain
Dx	CSF—motile, gram (+) bacilli	Lymphocytes predominate in CSF, ↓ glucose	Lymphocytes predominate in CSF, ↓ glucose, urease (+), yeast, India ink (+)	PCR of CSF, stool + serum
Rx	Ampicillin with or without aminoglycoside	2 months—isoniazid, rifampin, pyrazinamide + 10 months—isoniazid + rifampin	Amphotericin B + flucytosine	Supportive

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Central Nervous System

Meningoencephalitis

Age	Often children	Any	Any + AIDS <100 $CD4^+$ cells/mm
Type	Parasitic		
Agent	*Naegleria fowleri*	*Acanthamoeba castellani*	*Toxoplasma gondii*
Other clues	Diving in warm lakes, prefrontal headache, high fever, disturbance of smell	• Immunocompromised • Enters through skin	Ring enhancing lesion in brain of AIDS patient
Pathogenesis	Amebae forced through cribriform plate; direct spread to olfactory lobes	Spread via blood to brain	Intracellular parasite persists in immunoprivileged sites
Dx	Flagellated trophozoites in CSF	Star-shaped cysts in CSF	Serology, PCR
Rx	Amphotericin B (rarely successful)	Amphotericin B (rarely successful)	Pyrimethamine + sulfadiazine

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Central Nervous System

Encephalitis

(Fever, headache, changes in mental status, coma)

Age	**All**			
Type	Viral			
Agent	Herpes simplex I	Arboviruses: St. Louis, California, Eastern, Western, West Nile, and Venezuelan encephalitis viruses	Rabies	HIV
Other clues	Hemorrhagic necrosis of temporal lobe, RBC in CSF	Summer months, mosquito-borne	Negri bodies in hippocampal + Purkinje neurons of cerebellum, hallucination, excessive salivation	Microglial nodules, multinucleated syncytia
Pathogenesis	Perivascular cuffs, microglial nodules, neuron loss, neuronophagia			
Dx	PCR	PCR	Serology, RT-PCR	PCR or serology
Rx	Acyclovir	Supportive	None	Antiretroviral therapy

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Central Nervous System

Miscellaneous

Age	Any	Child	Any	
Type	Mass lesion	Reye syndrome	Epilepsy	Bell Palsy
Agent	*Streptococcus* or *Bacteroides*	Influenza, varicella	*Taenia solium*	*Borrelia burgdorferi*
Other clues	↑ Intracranial pressure, headache, nausea, vomiting, seizures; follows sinus, ear, dental infection	Aspirin use + vomiting, lethargy, irritability	Recent immigrant, travel to Mexico, exposure to swine; epilepsy of adult onset	Summer months, northeastern U.S. geography, tick exposure, target-shaped rash
Pathogenesis	Contiguous spread to brain	Unknown	Larvae encyst in brain (neurocysticercosis), calcifying lesions	Invades endothelial cells
Dx	Ring-enhancing lesion on CT	Clinical	CT, MRI serology	EIA + Western blot
Rx	Debridement, antibiotics	Supportive	Praziquantel, albendazole	Doxycycline

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Central Nervous System

Miscellaneous

Age	**Any**	
Type	Guillain-Barré syndrome	Progressive multifocal leukoencephalopathy (immuno-compromised/AIDS)
Agent	• *Campylobacter jejuni* (serotype O:19) • Influenza (1–3 weeks prior to onset)	JC virus
Other clues	Acute symmetric ascending inflammatory neuropathy begins in lower limbs and ascends; respiratory failure can occur in severe cases; autonomic dysfunction, cranial nerve involvement, sensory loss, pain, and paresthesias; reflexes decreased or absent; elevated CSF protein with normal cell count (albuminocytologic dissociation)	Varied neurologic symptoms, dementia, weakness, vision loss, impaired speech, intranuclear inclusions in oligodendrocytes
Pathogenesis	Molecular mimicry (?)	Demyelination, astrogliosis, lymphohistiocytosis
Dx	Clinical	Test for JC virus in CSF
Rx	Plasmapheresis, IVIGs	Invariably fatal

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Cardiac

Endocarditis

Janeway lesions (erythematous, nontender lesions on palms and soles),
Osler nodes (erythematous, tender lesions on fingers and toes, splinter hemorrhages,
Roth spots (retinal hemorrhages)

Type	Acute endocarditis (rapid onset, high fever, chills, chest pain)	Subacute endocarditis (insidious onset, previously abnormal valves, fatigue, low-grade fever, splinter hemorrhages)		
Agent	*Staphlyococcus aureus* (50%) Streptococci (35%)	*Streptococcus viridans* (55%)	*Staphylococcus epidermidis*	*Enterococcus*
Other clues	• Previously normal valves, tricuspid in IV drug users • Rapid onset	After dental surgery	IV drug abuser	Elderly male with prostate problems; patient with colon cancer
Pathogenesis	Highly virulent organism, PMN infiltration, abscesses, vegetations	Normal flora, oropharynx	Organisms with low virulence introduced into blood and grow on damaged valves	
Dx	Blood culture: • Staph: gram (+), catalase (+), coagulase (+) cocci • Strep: gram (+), catalase (–) cocci	Gram (+), catalase (–) coccus, α-hemolytic, lysed by bile, optochin sensitive	Gram (+), catalase (+), coagulase (–) coccus	Gram (+), catalase (–), PYR (+) coccus, esculin agar
Rx	Ceftriaxone, vancomycin	Penicillin, ceftriaxone	Penicillin and amino-glycoside	Penicillin, ceftriaxone

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Cardiac

	Endocarditis		Rheumatic Fever
Type	**Subacute endocarditis (insidious onset, previously abnormal valves, fatigue, low-grade fever, splinter hemorrhages)**		**Acute, type II hypersensitivity**
Agent	HACEK group: *Haemophilus aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*	*Candida albicans*	1–3 weeks after group A streptococcal (GAS) pharyngitis, 5–15 years old
Other clues	Gram (–) endocarditis	Patient with indwelling vascular catheter	**Jones criteria—major** • Carditis—may affect the endocardium, myocardium, or pericardium; myocarditis, causes most deaths during the acute stage • Erythema marginatum—macular skin rash, often in "bathing suit" distribution • Migratory polyarthritis—large joints that become red, swollen, and painful • Subcutaneous nodules • Sydenham chorea—involuntary, choreiform movements of the extremities **Jones criteria—minor** • Arthralgias • Elevated C-reactive protein • Elevated ESR • Fever • Leukocytosis • Previous rheumatic fever • Prolonged PR interval
Pathogenesis	• Normal flora of mouth • Organisms with low virulence introduced into blood and grow on damaged valves	Organisms with low virulence introduced into blood and grow on damaged valves	Antibodies made in response to streptococcal pharyngitis bind to cross-reactive Ag in heart, cause inflammation
Dx	Blood culture, gram (–) rods	Gram (+) yeast	• Antistreptolysin O titer (ASO) >200 • Jones criteria—2 major or 1 major and 2 minor
Rx	Ceftriaxone	Amphotericin B	Penicillin

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Cardiac

Rheumatic Heart Disease	Myocarditis (Hypertrophy and dilatation of all chambers, patchy hemorrhage, peripheral edema)			
Type	**Chronic result of inflammatory insult**	**Neutrophilic (bacterial)**	**Mononuclear (viral)**	**Parasitic (protozoal)**
Agent	GAS (ongoing autoimmune response)	Meningococcus or diphtheria (toxin mediated)	• Adenovirus • Enteroviruses (coxsackie B) • Also polio, rubella, influenza	*Trypanosoma cruzi*
Other clues	Mitral valve involved (75%–80%) fibrosis + stenosis, aortic valve secondary involvement	(See discussion of *Neisseria meningitidis* meningitis or diphtheria respiratory syndrome)	Potentially recurrent; may necessitate cardiac transplant	Immigrant from/ travel to South America; preceded by unilateral eyelid swelling (Romaña sign)
Pathogenesis	Aschoff bodies—perivascular fibrinoid necrosis with large histiocytes; Anitschkow cells, left atrial dilatation, mural thrombi, right ventricular hypertrophy			Dilated cardiomyopathy
Dx	Clinical		Serology	Trypomastigotes on blood film
Rx	Penicillin, erythromycin to prevent further GAS pharyngitis		Interferon α or β	Benznidazole, nifurtimox

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Gastrointestinal

Inflammatory Diarrheas
(Invasive organisms that cause fever, blood, and pus in stool; all patient age groups.)

Source	Poultry, domestic animals, water		Milk, wild and domestic animals, fecal-oral	Associated with antibiotic use (clindamycin)
Agent	*Campylobacter jejuni* (No. 1 bacterial diarrhea in U.S.)	*Salmonella* spp. (non-typhoidal Salmonellae)	*Yersinia enterocolitica*	*Clostridium difficile*
Incubation	3–5 days	8–48 hours	2–7 days	N/A
Pathogenesis	Invades epithelium	Penetrates to lamina propria of ileocecal region → PMN response and prostaglandin synthesis, which stimulates cAMP	Cold-climate pseudoappendicitis; heat-stable enterotoxin; arthritis may occur	Pseudomembranous colitis, normal flora organism overgrows when competitors killed
Dx	Oxidase (+), gram (–), curved rod, seagull-wings shape; grows at 42°C; microaerophile	Gram (–), motile rod; nonencapsulated, oxidase (–)	Gram (–), motile rod; nonencapsulated, oxidase (–), urease (+); bipolar staining; best growth at 25°C	Gram (+) rod, anaerobic spore former
Rx	Treatment for severe cases only; erythromycin for invasive disease	Severe cases only; sensitivity testing required	Sever cases only; aminoglycosides, trimethoprim-sulfamethoxazole	Switch antibiotic; metronidazole

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Gastrointestinal

Inflammatory Diarrheas

(Invasive organisms that cause fever, blood, and pus in stool; all patient age groups.)

Source	**Food, water, fecal-oral**		
Agent	Enteroinvasive *E. coli*	*Shigella* spp.	*Entamoeba histolytica* (typically ingested during foreign travel, often Mexico)
Incubation	2–3 days	1–7 days	2–4 weeks
Pathogenesis	Shallow mucosal ulcerations and dysentery; septicemia rare		Trophozoites invade colon; flask-like lesions, extraintestinal abscesses (liver)
Dx	Gram (–) rod; motile, lactose fermenter; serotyping compares O, H, K antigens	Gram (–) rod; nonlactose fermenting; nonmotile	Motile trophozoites or quadrinucleate cysts
Rx	Sensitivity testing required	Severe cases only: Fluoroquinolones, trimethoprim-sulfamethoxazole	Metronidazole

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Gastrointestinal

Noninflammatory Diarrheas

(Intoxication; pre-formed toxin is ingested; no fever, blood, or pus; all patient age groups.)

Source	Ham, potato salad, cream pastries	Fried rice	Meat, vegetables
Agent	*Staphylococcus aureus*	*Bacillus cereus* (emetic form)	*Bacillus cereus* (diarrheal form)
Incubation	<6 hours		18 hours
Pathogenesis	Heat-stable enterotoxin is produced in food (contamination by food handler with skin lesions); food sits at room temperature	Heat-stable toxin causes vomiting	Heat-labile toxin causes diarrhea (similar to *E. coli* LT)
Dx	Symptoms, time of onset, food source	Symptoms, time of onset, food source	Symptoms, time of onset, food source
Rx	Recovery without treatment	Recovery without treatment	Recovery without treatment

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Gastrointestinal

Noninflammatory Diarrheas (Noninvasive organisms; no fever, no blood, no pus.)				
	Infants and toddlers		Children, immunocompromised	
Source	**Food, water, fecal-oral**		**Day care, fecal-oral, animals, homosexuals**	**Nosocomial**
Agent	Rotaviruses	Enteropathogenic *E. coli* (EPEC) (often ingested during travel to/from developing countries)	*Cryptosporidium parvum*	Adenovirus, types 40/41
Incubation	1–3 days	2–6 days	2–4 weeks	7–8 days
Pathogenesis	Microvilli of small intestine blunted; dehydration	Adherence to enterocytes through pili → damage to adjoining microvilli	Parasites intracellular in brush border	Death of enteric cells causes diarrhea
Dx	Diagnosis by exclusion; dsRNA naked, double-shelled, icosahedral (Reovirus family)	Gram (–) rod; motile; lactose fermenter; serotyping compares O, H, K antigens	Acid-fast oocytes in stool	Diagnosed by exclusion: naked, dsDNA, icosahedral
Rx	Supportive	Sensitivity testing required	Nitazoxanide, puromycin, azithromycin in immunocompromised	No specific therapy

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Gastrointestinal

Noninflammatory Diarrheas

(Noninvasive organisms; no fever, no blood, no pus; all patient age groups.)

Source	Beef, poultry, gravies, Mexican food	Raw or under-cooked shellfish	Food, fecal-oral (hamburger)	Water, food, fecal-oral
Agent	*Clostridium perfringens*	*Vibrio parahaemolyticus*	Enterohemorrhagic *E. coli* (EHEC)	*Vibrio cholerae*
Incubation	8–24 hours	5–92 hours	3–5 days	9–72 hours
Pathogenesis	Enterotoxin	Self-limited gastroenteritis mimicking cholera	Verotoxin, which inhibits 60S ribosomal subunit, causes bloody diarrhea; no fever	Toxin stimulates adenylate cyclase; rice water stools
Dx	Anaerobic, gram (+) rods, spore forming	Curved, gram (–) rod; oxidase (+); "shooting-star" motility	Gram (–) rod; motile; lactose fermenter; serotyping compares O, H, K antigens; O157H7 most common; does not ferment sorbitol	Curved, gram (–) rod; oxidase (+); "shooting-star" motility
Rx	Not indicated		Antibiotics may increase risk of hemolytic-uremic syndrome	Oral rehydration therapy; tetracycline shortens symptoms

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Gastrointestinal

Noninflammatory Diarrheas

(Noninvasive organisms; no fever, no blood, no pus; all patient age groups.)

Source	**Water, food, fecal-oral**		
Agent	Enterotoxigenic *E. coli* (ETEC)	*Norwalk virus* (or *Norovirus* and Norwalk-like virus)	*Giardia lamblia* (often ingested from fresh water sources during camping)
Incubation	12–72 hours	18–48 hours	5–25 days
Pathogenesis	Heat-labile toxin (LT) stimulates adenylate cyclase; stable toxin stimulates guanylate cyclase	Blunting of microvilli; "cruise ship" diarrhea	Cysts ingested; trophozoites; multiply and attach to small intestinal villi by sucking disc, cause fat malabsorption → steatorrhea
Dx	Gram (–) rod; motile; lactose fermenter; serotyping compares O, H, K antigens	Diagnosis by exclusion: ss(+)RNA, naked, icosahedral (Calicivirus family)	Flagellated binucleate trophozoites; "falling-leaf" motility; quadrinucleate cysts
Rx	Sensitivity testing required	Supportive	Metronidazole

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Gastrointestinal

Hepatic

Hepatitis

(Increased liver function tests, malaise, anorexia, nausea, right upper quadrant pain, jaundice.)

Source	Food borne		Sexual/parenteral	
	U.S.	Africa/Asia		
Agent	Hepatitis A virus: Infectious hepatitis, picornavirus; naked, ss(+)RNA	Hepatitis E virus: Enteric hepatitis hepevirus; naked, ss(+)RNA	Hepatitis B virus: "Serum hepatitis" hepadnavirus; enveloped DNA	Hepatitis C virus: "Post-transfusion" hepatitis flavivirus; enveloped ss(+)RNA
Other clues	Raw oysters, no chronicity	Pregnant women, 20% fatality, no chronicity	IV drug use, chronicity, carcinoma	Prison-system, high chronicity, carcinoma
Pathogenesis	Virus is cytopathic		CMI is cytopathic; carcinogenesis from DNA integration	Chronic cell damage → cirrhosis and carcinogenesis
Dx	Serology		• Serology • $HBsAg^+$ • $HBcAb^+$	Serology
Rx	Supportive		Interferon α	Interferon α, ribavirin

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Gastrointestinal

Hepatic			
	Hepatitis		**Cirrhosis** (Chronic scarring + fibrosis → ↑ portal pressure → varices → rupture → hematemesis)
Source	**Sexual/parenteral**		**Chronic hepatitis B, C, D, or skin penetration by cercariae**
Agent	Hepatitis D Delta agent (defective virion; requires complementation of envelope from hepatitis B)		*Schistosoma* spp. (or see discussion of hepatitis B, C, and D)
Other Clues			Travel history: Tropics, Africa, Asia; 10% of population of Puerto Rico is infected
Pathogenesis	Coinfection—hepatitis B and delta agent acquired at same time; no greater risk of chronicity	Superinfection—delta agent acquired in chronic hepatitis B → fulminant disease (massive hepatic necrosis + dysfunction mortality 25%–90%)	Eggs block portal triads → fibrosis from granulomas
Dx	Serology: HBsAg + Abα Delta agent		Spined eggs in stool
Rx	Interferon α, lamivudine		Praziquantel

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Gastrointestinal

Hepatic

Abscess (Mass Lesion)

Source	Seeding from bacteremia	Fecal-oral	
Agent	Bacterial (*E. coli, Klebsiella Streptococcus, Staphylococcus*)	*Entamoeba histolytica*	*Ascaris lumbricoides*
Other clues	Ascending cholangitis	• Men >40 following diarrheal disease • Mexico • "Anchovy paste" fluid	• Blockage of bile ducts • Eosinophilia
Pathogenesis	Blood-borne spread from intestine		• Adults • Migrate to extraintestinal sites in heavy infections
Dx	Blood culture	• Cysts or trophs in feces or none • Scintigraphy • Serology	Eggs in stool—large, oval, rough-shelled
Rx	Depends on agent cultured	Metronidazole + dilanoxanide furoate	Surgery

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Gastrointestinal

	Hepatic			Pancreatic
	Bile Duct Blockage		Cholangiocarcinoma	Pancreatitis
Source	**Fecal-oral**	**Ingestion of water plants**		**Respiratory droplets**
Agent	*Ascaris lumbricoides* (large roundworm)	*Fasciola hepatica* (sheep liver fluke)	*Clonorchis sinensis* (Chinese liver fluke)	Mumps virus (Paramyxovirus)
Other clues	Abdominal pain, distention, jaundice, weight loss	Outside of U.S.; rural, exposure to sheep	Weight loss, jaundice, pruritis	• With parotitis, fever • Unvaccinated • Orchitis in older males
Pathogenesis	Blockage of bile ducts		Primary sclerosing cholangitis	Virus attacks glandular tissue
Dx	Large, oval rough-shelled eggs in stool	Operculated eggs in stool		Serology PCR
Rx	Surgery	Triclabendazole		Supportive

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Gastrointestinal

Acute Abdominal Pain

Source	Intestinal blockage fecal-oral		Peritonitis
Agent	*Ascaris lumbricoides*	*Diphyllobothriium latum*	Mixed normal flora (*Bacteroides*, *E. coli*)
Other clues	Child, rural South	Ingestion of raw fish; Great Lakes region; megaloblastic anemia	Bowel trauma, age, cancer
Pathogenesis	Large worm blocks intestine in heavy infections	Tapeworm grows to 3 m, competes for vitamin B12	Spread out of intestine from damage
Dx	Large, oval rough-shelled eggs in stool	Operculated eggs in stool	Culture blood
Rx	Surgery	Praziquantel	Metronidazole

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Urinary/Renal

Urethritis

Culture results	Gram (–) diplococci in PMNs, growth on Thayer-Martin agar, DNA probes	Tissue culture; glycogen-containing inclusion bodies in cytoplasm	Urease (+), no cell wall; not Gram-staining; diagnosed by exclusion, urinary pH ↑	Flagellated protozoan; corkscrew motility
Agent	*Neisseria gonorrhoeae*	*Chlamydia trachomatis*	*Ureaplasma urealyticum*	*Trichomonas vaginalis*
Pathogenesis	Invasive, pili assist adherence; have antigenic variation; are antiphagocytic; IgA protease	Obligate intracellular in epithelial cells; CMI and DTH cause scarring	Urease raises pH of urine → struvite stones	Unknown, PMN filtrate
Rx	Ceftriaxone	Tetracyclines, macrolides		Metronidazole

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Urinary/Renal

Cystitis

(Urinary frequency, urgency, dysuria, suprapubic pain, no WBC casts in urine.)

Culture results	Culture of urine ≥10^5 CFU/mL of gram (–) rods in urine	Culture of urine, gram (+) cocci "honeymoon cystitis"	Culture of urine, lactose non-fermenting gram (–) bacilli with swarming motility ↑ urinary pH
Agent	*E. coli* (No. 1 cause), other gram (–) enterics	*Staphylococcus saprophyticus*	*Proteus* spp.
Pathogenesis	Pili, adhesins, motility, many are β-hemolytic	Sexual intercourse introduces normal flora organisms into urethra	Urease raises urinary pH, predisposes to struvite stones
Rx	Fluoroquinolones, sulfonamide	Fluoroquinolones, TMP-SMX	Fluoroquinolones

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Urinary/Renal

Pyelonephritis
(Previous + flank pain, fever + WBC casts)

Culture results	Gram (–) lactose fermenting nitrite (+) bacillus	Gram (–) swarming non-lactose fermenting bacillus	Gram (–) lactose fermenting bacillus
Agent	*Escherichia coli*	*Proteus mirabilis*	*Klebsiella* spp.
Pathogenesis	Pili mediate adherence; motility	Urease raises urinary pH + predisposes to struvite stones	Large capsule
Rx	Fluoroquinolones, 3rd-generation cephalosporin, ampicillin-sulbactam		

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Urinary/Renal

Poststreptococcal Glomerulonephritis

Vignette clues	**Nephritis; elevated ASLO; low complement; children > adults. Usually recover completely; occasionally progresses to RPGN.**
Agent	*Streptococcus pyogenes* (post-infectious sequela)
Pathogenesis	• Immunologic (type III hypersensitivity) • Polymorphonuclear neutrophil leukocyte infiltration; proliferation
Dx	Granular pattern; GBM and mesangium contain IgG and C3; subepithelial humps
Rx	Symptomatic

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Reproductive

STIs: Lesions of the External Genitalia

Condition	Vulvovaginitis (vaginal discharge + inflammation)			Chancroid
Characteristics	Adherent yellowish discharge, pH >5, fishy amine odor in KOH, clue cells, gram (–) cells dominate	Vulvovaginitis, pruritus erythema, discharge with consistency of cottage cheese	"Strawberry cervix," foamy, purulent discharge; many PMNs and motile trophozoites microscopically (corkscrew motility)	Soft, painful ulcer, suppurative with adenopathy; slow to heal
Agent	*Gardnerella vaginalis* (bacterial vaginosis)	*Candida* spp.	*Trichomonas vaginalis*	*Haemophilus ducreyi*
Pathogenesis	Overgrowth of anaerobic bacteria	• Immunocompromised patient • Antibiotic use leads to fungal overgrowth	Unknown	
Dx	Clue cells, gram (–) rods	Germ tube test, gram (+) yeasts in vaginal fluids	Pear-shaped trophozoites with corkscrew motility	Gram (–) rods, chocolate agar (requires NAD and hemin)
Rx	Metronidazole	Nystatin, miconazole	Metronidazole	Cefotaxime, ceftriaxone

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Reproductive

STIs: Lesions of the External Genitalia

Condition	Lymphogranuloma venereum	Primary syphilis	Secondary syphilis	Tertiary syphilis
Characteristics	Soft, painless papule heals, lymph nodes enlarge and develop fistulas, genital elephantiasis may develop	Painless chancre forms on glans penis (or vulva/cervix) and heals within 1–3 months	Local or generalized rash lasting 1–3 months, can involve the palms and soles	Affects central nervous system, heart, and skin; characteristic lesion is gumma, may be single or multiple; most common in the liver, testes, and bone
Agent	*Chlamydia trachomatis* serotypes L1–3	*Treponema pallidum*		
Pathogenesis	Obligate intracellular	3-week incubation during which spirochetes spread throughout the body	Develops 1–2 months after primary stage	Develops in one-third of untreated patients; *neurosyphilis*: meningovascular, tabes dorsalis, and general paresis; obliterative endarteritis of vasa vasorum of the aorta
Dx	Cell culture, glycogen-containing inclusions	Biopsy/scraping viewed with dark-field microscopy shows spirillar organisms	Serology—VDRL (+) (nonspecific); FTA-ABS (specific)	Serology—FTA-ABS, nonspecific tests may be negative
Rx	Tetracyclines, erythromycin	Penicillin, doxycycline is an alternative		

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Reproductive

STIs: Lesions of the External Genitalia

Condition	Condyloma acuminatum (genital warts)	Genital herpes
Characteristics	Lesions are papillary/wart-like; may be sessile or pedunculated; koilocytotic atypia is present; anogenital	Multiple, painful, vesicular, coalescing, recurring
Agent	Human Papillomavirus (HPV, most common STD in U.S., typically types 6 and 11)	Herpes simplex (usually type 2)
Pathogenesis	• HPV proteins E6 and E7 inactivate cellular antioncogenes • Associated with cervical cancer (types 16 and 18)	Latent virus in sensory ganglia reactivates
Dx	dsDNA, naked, icosahedral, intranuclear inclusion bodies	Virus culture, intranuclear inclusions, syncytia (Tzanck smear), dsDNA enveloped (nuclear), icosahedral
Rx	Podophyllin, imiquimod	Acyclovir, valacyclovir, famciclovir

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Reproductive

Cervicitis and Cancer

Condition	Cervicitis	Cervicitis	Cervicitis	Cervical carcinoma
Characteristics	Friable, inflamed cervix with mucopurulent discharge			Third most common malignant tumor of the female genital tract in U.S.; peak incidence in the 40s
Agent	*Neisseria gonorrhoeae*	*Chlamydia trachomatis*	Herpes simplex virus	HPV types 16, 18, 31, and 33 (also associated with early first intercourse, multiple sexual partners, smoking, and immunosuppression)
Pathogenesis	Invades mucosa, PMN infiltration, pili, IgA protease	Obligate intracellular; CMI and DTH → scarring	Vesicular lesions, painful	Begins as cervical intraepithelial neoplasia (CIN) → carcinoma in situ → invasive squamous cell cancer
Dx	Gram (–) diplococci, Thayer-Martin agar	Tissue culture, cytoplasmic inclusions	dsDNA, nuclear envelope, icosahedral; Tzanck smear, intranuclear inclusions	• May be asymptomatic, or may have postcoital bleeding, dyspareunia, discharge • Early detection possible with Papanicolaou (Pap) smear—koilocytic cells
Rx	Ceftriaxone	Tetracyclines, macrolides	Acyaclovir, valacyclovir, famciclovir	Cryotherapy

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Reproductive

Condition	Endometritis	Pelvic inflammatory disease	
Characteristics	Associated with pregnancy or abortions (acute) Associated with PID and intrauterine devices (IUDs) (chronic)	Adnexal tenderness, bleeding, dyspareunia, vaginal discharge, fever, chandelier sign, onset often follows menses	
Agent	*Bacteroides, Chlamydia trachomatis, Gardnerella,* group B streptococcus, *Ureaplasma, Peptostreptococcus*	*Neisseria gonorrhoeae*	*Chlamydia trachomatis* (No. 1 bacterial STI)
Pathogenesis	• Ascending infection from the cervix • Endometrium and decidua	Pili and IgA protease production	Intracellular in mucosal epithelia; causes type IV hypersensitivity damage
Dx	Culture	Gram (–) diplococci in PMNs or culture on Thayer-Martin	Tissue culture, intracytoplasmic inclusions in mucosal cells
Rx	Depends on agent	Ceftriaxone + doxycycline (doxycycline given for presumed coinfection with *Chlamydia*)	Doxycycline, macrolides

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Reproductive

Infections That Cross the Placenta

(Mnemonic **TORCHeS**: **T**oxoplasma, **O**ther, **R**ubella, **C**MV, **He**rpes/HIV, **S**yphilis)

Condition	CMV	Congenital rubella syndrome (CRS)	Congenital syphilis	Toxoplasmosis	Hydrops fetalis
Characteristics	Thrombocytic purpura, hepato-splenomegaly, microcephaly	Patent ductus arteriosus, pulmonary stenosis, sensorineural hearing loss, cataracts	Maculopapular rash, rhinorrhea, dactylitis, osteochondritis periostitis	Hydrocephalus diffuse intracranial calcification chorioretinitis	Diffuse edema (hydrops fetalis)
Agent	CMV (No. 1 in utero infection)	Rubella	*Treponema pallidum*	*Toxoplasma gondii*	Parvovirus B19
Pathogenesis	Pathogen crosses the placenta and destroys fetal tissues				Virus destroys bone marrow erythrocyte precursors
Dx	PCR		Serology VDRL, FTA-ABS	Serology	Virus culture
Rx	Antivirals, supportive	Supportive	Penicillin G, azithromycin, 3rd-generation cephalosporin	Atovaquone, clindamycin	Intravenous immunoglobulin therapy

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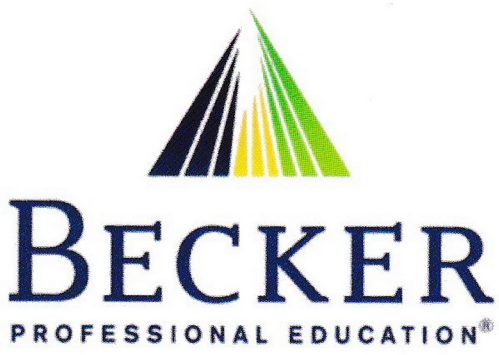
USMLE STEP 1 REVIEW



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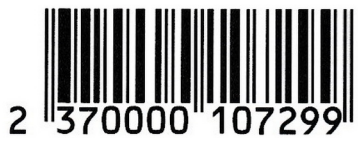
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